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FRACTURES OF THE FOREARM AND ELBOW IN CHILDREN*

An Analysis of Three Hundred and Sixty-Four Consecutive Cases

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IN making a study of children's fractures, one cannot but realize that growing bone, epiphyses and the extraordinary power of repair are major factors to be considered. However, there is no reason because of this reparative power that the surgeon or medical man treating these cases should be satisfied with a poor anatomic reduction. One often hears it said that if half the surface of a fractured bone fragment is in apposition, Nature will produce a satisfactory result. With the growing demand of the public for better medical and surgical care, it behooves physicians to be satisfied only with the product of their very best effort. Today, there should be no half-way measures in fracture therapy.

The subject of this communication covers an important region of the child's body, a region involved most commonly in fractures. Beekman and Sullivan[1] report, in a series of over 2000 fractures in children, that 75 per cent were in the long bones of the upper extremity and that the radius was the most frequently fractured long bone in the body. The clavicle has usually been considered to be commonly injured, but it represented less than 8 per cent in their series. Figures will doubtless vary in different age groups of children, the clavicle being certainly the most commonly fractured bone at birth.[2] However, this paper is concerned with the age group from one day to twelve years.

During the last three and a half years, 364 consecutive cases of fracture of the forearm or elbow have been treated at the Children's Hospital. Of these, the distal third of the forearm was involved in 200 cases, the middle and proximal thirds of the forearm in 58, and the elbow, including the head and neck of the radius and olecranon, in 106. From this series, dislocations of the distal radial epiphysis are omitted, being more properly included in wrist rather than forearm fractures.

In the treatment of fractures in the growing child, one should always be guarded in giving a prognosis, particularly when injuries to the epiphyses are involved. Aitken[3] has analyzed these fractures and has drawn some good conclusions. Abbott[4] has ascertained by a practical arithmetic formula the expected growth of a shaft attached to a damaged epiphysis. To interfere with normal growth, the fracture must pass through the cartilage plate and injure the proliferating cells. Separation of an epiphysis does not ordinarily injure these cells.

FRACTURES OF DISTAL THIRD OF FOREARM

The character of bone in the growing child is such that a long-bone fracture is often incomplete. In this series of 200 cases of fracture of the distal third of the forearm, 102 (51 per cent) had incomplete fractures, either subperiosteal or true greenstick in character; of 58 cases with fracture of the middle or upper third of the shaft of the forearm, 16 (28 per cent) had incomplete fractures; and of 106 cases with elbow fractures, 23 (22 per cent) had incomplete fractures. Thus, it appears that the more distal the fracture of the forearm, the greater is the likelihood of an incomplete fracture.

The treatment of these incomplete fractures is aimed at restoring proper anatomic alignment. A simple subperiosteal crack or impaction where the alignment remains normal needs no manipulative correction, merely fixation. The greenstick

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shaft fracture with angulation requires manipulation, and often sufficient force to break the shaft completely through, to attain alignment, before fixation is applied. There are exceptions, however, even to this — notably greenstick fractures of the clavicle.

The necessity for surgical intervention in the treatment of fractures in this region should be determined by judgment acquired by experience. Beekman and Sullivan,[1] Whipple and St. John,[5] Ashurst[6] and Bosworth[7] agree that open reduction is rarely indicated. However, when necessary, it should be performed within forty-eight hours of the failure of closed reduction, with meticulous aseptic technic and with a minimum of trauma. At the Children's Hospital, we have never resorted to the use of bone plates, screws or other forms of advertised hardware; a reposition of fragments and periosteal suture, and occasionally wire suture, are employed. In only 2 (1 per cent) of the cases with fracture of the distal third of the forearm, six weeks and three weeks old, respectively, was open reduction necessary.

The art and science of closed manipulative reduction followed by proper fixation seem to be fast disappearing from the present era of surgical development. Admittedly, not all fractures can be adequately reduced by closed reduction, but the temptation to obtain anatomic alignment by open reduction is great in this age of gadgets. The aim of treatment is perfect function and as nearly as possible anatomic realignment and continuity. However, malunion and nonunion require all that surgical skill can provide — a different phase of fracture therapy. Compound fractures require careful débridement and surgical care. As yet, we have not adopted the Orr[8] or Trueta[9] method and can report that our 2 cases of compound fracture in this series (both in the distal third of the radius) healed by primary union.

The treatment that we recommend consists in early closed reduction, followed by adequate fixation. In fractures of the distal third of the forearm, not a Colles in children, some resort to the fluoroscope as an aid, but the cautious technician uses this piece of apparatus very seldom. Digital palpation and observation should assist one in ascertaining the proper alignment, and fixation should be promptly applied. X-ray films must be taken promptly after reduction and the application of fixation, not only to satisfy the surgeon of his manipulation, but also to serve as a safeguard against possible future litigation. Fixation is usually applied with molded plaster splints with the hand in semipronation; the plaster is carried around the elbow in true "sugar-tongs" fashion if it is believed that the mobility of the upper fragments should be limited (Fig. 1).* Board splints are still used, and give excellent results when properly applied.

When these patients are ambulatory in a sling,

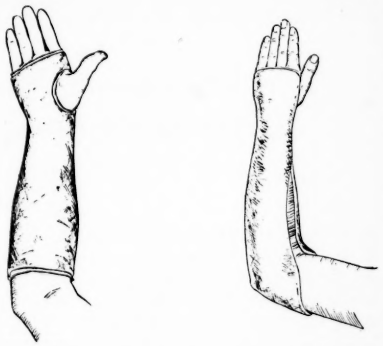

FIGURE 1. *Fractures of the Distal Third of the Forearm Treated with a Molded Plaster Splint.*

A cylinder is used in A, *and a typical "sugar tongs" in* B.

one should follow them at least twice a week, removing and repadding and adjusting the splints at regular intervals. The posterior splint should be removed after three weeks, the anterior splint after four weeks, and the sling after six weeks.

TABLE 1. *Results of Treatment in Fractures of the Distal Third of the Forearm.*

TYPE OF FRACTURE	NO. OF CASES	CASES REDUCED	RESULTS	
			GOOD	INADEQUATE FOLLOW-UP
Both bones (incomplete)	42	31	27	15
Both bones (complete)	56	52	40	16
Radius (complete) and ulna (incomplete)	9	8	6	3
Radius (incomplete)	49	16	39	10
Radius (complete)	31	20	26	5
Miscellaneous (subperiosteal)	13	0	11	2
Totals	200	127	149	51

In our series, there were 9 cases of refracture between one month and five years following the original injury.

Table 1 presents the results of treatment in fractures of the distal third of the forearm.

FRACTURES OF PROXIMAL TWO THIRDS OF FOREARM

In fractures of the proximal two thirds of the bone shafts of the forearm, early reduction and

*Surgeons experienced in the use of the more recently developed plastic materials (Castex and Thermex) may substitute these light waterproof molded splints for plaster of Paris.

adequate fixation are essential. Careful closed manipulation, with fluoroscopy as an aid, must be promptly carried out. In this portion of the forearm, palpation is less accurate, and x-ray visualization is of value. Whipple and St. John[5] have

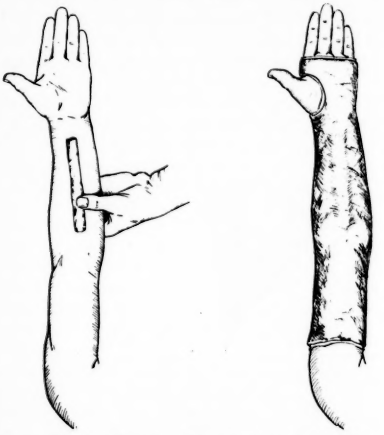

FIGURE 2. *The Use of a Plaster-Bandage Roll, over the Flexor Surface of the Forearm, as an Extra Aid to Fixation in Fractures of the Proximal Two Thirds of the Forearm.*

recommended full supination of the hand as the position for fixation, with the elbow flexed to 90°, and an internal angular splint of metal. Plaster of Paris is now the customary splinting material, and is put on as a full cylinder from the knuckles

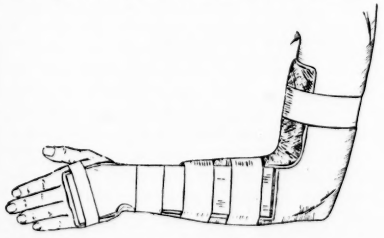

FIGURE 3. *The Use of Internal Angular and Board Splints for Immobilization of Fractures of the Proximal Third of the Forearm.*

Supination rather than the neutral position may be substituted.

to the axilla, with the hand in supination and the elbow in extension or in right-angle flexion (Figs. 2 and 3). It is impossible to set any hard and fast rule for the latter, because no two cases are exactly alike and each is an individual problem. Flexion will hold some, but not all. The use of a narrow roll of plaster bandage placed between the layers of plaster on the flexor surface of the supinated forearm in the area of the interosseous membrane does assist in holding these bones in alignment. A sling is used when the elbow is fixed at 90° flexion.

It is best to leave the original plaster for three or four weeks and then secure partial immobilization in molded plaster splints for another two or three weeks. Beekman and Sullivan[1] recommend fixation for eight weeks, because of the apparent likelihood of refracture. Although this period seems long to us, it is safe, but will not prevent all refractures. Our series of 58 patients

TABLE 2. *Results of Treatment in Fractures of the Proximal Two Thirds of the Forearm.*

Type of Fracture	No. of Cases	Cases Reduced	Results	
			Good	Inadequate Follow-up
Both bones (incomplete)	10	10	5	5
Both bones (complete)	28	28	26	2
Radius (complete) and ulna (incomplete)	3	3	3	–
Radius (incomplete)	5	5	4	1
Radius (complete)	6	4	6	–
Ulna (incomplete)	1	–	–	1
Ulna (complete)	5	5	3	2
Totals	58	55	47	11

with fractures of the upper two thirds of the forearm includes one with refractures at the original site three times in three years, 2 cases with refracture in two years, and 4 cases with refracture between three months and thirty-three months after the original injury. Of this entire group, not one case required open reduction. On the whole, the results of this method of treatment are entirely satisfactory (Table 2).

Fractures of Elbow

In fractures of the elbow, particularly those of the distal end of the humerus, one should follow the principles set down by Ashurst[6] in 1910 and emphasized again by Ladd[10] in 1916. The results are surprisingly good with conservative treatment, although one should remember that if premonitory signs and symptoms of Volkmann's ischemic contracture appear within the first twenty-four hours, the fracture should be "taken down," the skin prepared, and open reduction and evacuation of the hematoma performed within forty-eight hours. In all types of fractures, Ashurst with 56 cases had 81 per cent "perfect" results, and Ladd with 45 cases had 91 per cent. In the purely supracondylar and transcondylar types, their results are even better. The problem comes down to a definition of the adjective "perfect." We consider that perfect function entails no greater total loss of

combined flexion and extension than 10° (a maximum limitation of 5° each), with normal supination and pronation and a carrying angle with a cubitus varus or valgus of only slight degree if any. Since there is a variation in elbow function in every person, one must compare the patient's normal elbow with the injured when arriving at any definite conclusion. A skillful reduction must be performed early, before too much swelling is apparent, and the fixation must hold the reduced fragments in position.

As a general rule, we use the acute flexion position in all elbow fractures except those of the olecranon. We maintain the position by the use of adhesive plaster and the so-called "pistol-holster" sling (Fig. 4), thereby leaving the fingers, hands and radial pulse readily palpable. By untying the sling from behind the neck, the elbow itself is made visible without loss of the fixation. All patients with elbow fractures should be hospitalized for at least twenty-four hours after reduction. Dunlop[11] has described a method of adhesive bed traction with which we have had no experience, but according to Ashurst[6] this should not reduce the distal fragment of the transcondylar type completely. It undoubtedly might be a useful method in fractures that are badly swollen, with blebs in the skin, and those that are twenty-four hours old.

In supracondylar and transcondylar fractures of the humerus, the reduction is carried out under a general anesthetic by a gentle rocking motion of the elbow in hyperextension, properly to align and engage the fragments in the anteroposterior plane, and then hyperflexion so that the fingers of the hand rest on the acromioclavicular joint of the shoulder. The arm is held in that position while the bony landmarks are identified and compared with those of the normal elbow in hyperflexion and while the circulation in the fingernails and radial pulse is checked. If reduction is incomplete, the fingers will not rest on the shoulder, and the radial pulse will be lost and the maneuver must then be repeated, thumb pressure on the distal fragment being exerted during the flexion stage. Fluoroscopy is of considerable assistance in cases presenting marked swelling. The maneuver does not require force to attain reduction. Once the adhesive-tape fixation is applied, x-ray films should be taken in both planes, and if the position is good, the pistol-holster sling is applied and

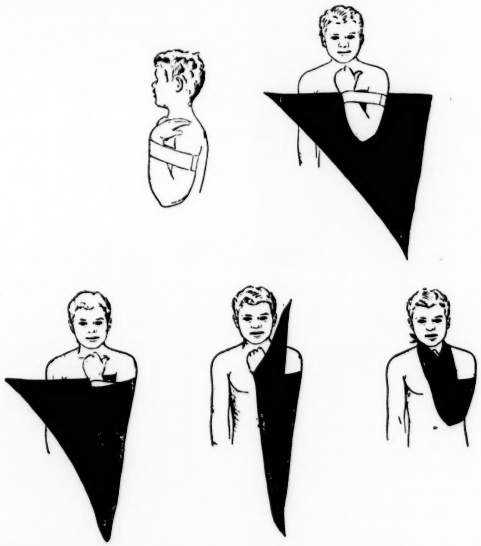

FIGURE 4. *The Acute Flexion Position for Fractures of the Elbow, except Those of the Olecranon, Using Adhesive-Tape Fixation, with the Pistol-Holster Sling.*

the child put to bed. The postoperative orders should require an hourly check on the pulse and circulation of the wrist, hand and fingers. Among the 58 reductions of transcondylar and supracondylar fractures of the humerus, there was 1 open reduction; furthermore, in 20 of these cases, there was gross displacement, usually medial and posterior, of the distal fragment.

The reduction of fractures of the lateral and medial epicondyles and of the T fracture should be manipulated in much the same way, but one should rely more on digital pressure to replace them. The badly displaced fractures are difficult and require operative reduction and suture in position. Beekman and Sullivan[1] do not hesitate to operate because the carrying angle is so affected by an improperly replaced condyle. With the acute flexion position, it is the tightly drawn fascial envelope of the triceps muscle that holds these fragments in place. Guarded prognoses should always be given in these cases, because the epiphyseal cartilage plate has been damaged.

Fractures of the head and neck of the radius enter the joint, and radical surgery (excision of the head) in a growing child always results in a crippled elbow joint. The healing that takes place in a slightly displaced head of the radius is remarkable, provided the two fragments touch at all, and it is preferable to be ultraconservative. In this series, we had 3 cases of complete displacement of the head from the neck of the radius.

Olecranon fractures in children are rarely complete, with separation of the fragments. This occurred in none of the 4 cases in the series. If separation occurs in the growing child, however, we prefer operative reduction and suture of the overlying fascia; no hardware should be used.

When acute flexion position is utilized, this position and fixation should be maintained for three weeks; of course, the skin should be checked and cared for twice a week during that period. For the following week, a triangle sling is used under the clothing, and the elbow carried at 90° flexion. For the fifth week, the sling is carried outside the clothing, and at six weeks the arm is free. Physiotherapy should never be employed in the convalescent care of elbow fractures in children, and Nature should be allowed her opportunity to absorb excess callus and to improve motion. Forced manipulation should never be used in an attempt to increase motion. End results are not always obtained until eighteen to twenty-four months after the original fracture.

The end results of the 106 fractures of the elbow treated according to these general principles are presented in Table 3. Of the unsatisfactory results in 8 cases, the fractures were in the head and neck of the radius in 2, in the region of the lateral condyle in 3 (2 of these were old united fractures when the patients came to the hospital and had originally been treated elsewhere), supracondylar in 2 (1 of which was a month old on entry), and an old transcondylar fracture in 1. Therefore, excluding the old fractures, there were 5 unsatisfactory end results in 98 cases of elbow fracture, or an incidence of 5 per cent.

One should face the problem of elbow fractures in children with meticulous care and courage, for on the whole the results are quite satisfactory. The problem of operative correction of bony deformity in a healed elbow fracture is tempting, but it is a better policy to await the full growth of the child before such corrections are attempted. To damage the growing cartilage plate by operative interference because of a false carrying angle or prominent condyle is foolhardy, meddlesome surgery.

In this series of 106 fractures of the elbow in which 102 reductions were carried out, there were 8 open reductions after attempted closed reduction had failed. The results are given in Table 4. Open reduction was attempted in two old fractures (more than one month after the injury), and in each case there was a poor result. Two out of 3 cases of fractures of the head and neck of the radius with displacement of the fragments resulted poorly. From this small incidence of open

TABLE 3. *Results of Treatment in Fractures of the Elbow.*

TYPE OF FRACTURE	NO. OF CASES	CASES REDUCED	RESULTS		
			GOOD	POOR	INADEQUATE FOLLOW-UP
Transcondylar (humerus)	50	47	45	1	4
Supracondylar	12	12	8	2	2
Lateral condyle and epicondyle	21	21	17	3	1
Medial condyle and epicondyle	7	7	7	–	–
T	2	2	2	–	–
Head and neck of radius	10	10	7	2	1
Olecranon	4	4	4	–	–
Totals	106	102	90	8	8

TABLE 4. *Results of Treatment by Open Reduction in Fractures of the Elbow.*

TYPE OF FRACTURE	NO. OF NEW CASES	NO. OF OLD CASES	RESULTS	
			GOOD	POOR
Transcondylar	1	1	1	1
Lateral condyle and epicondyle	1	1	1	1
Medial condyle and epicondyle	1	–	1	–
Head and neck of radius	3	–	1	2
Totals	6	2	4	4

reductions, we can conclude that open reduction need rarely be resorted to and only then at an early period (within forty-eight hours after the injury) following an unsuccessful attempted closed reduction.

Complications

Although Volkmann's ischemic contracture is a serious complication in fractures of the elbow and forearm, in this series of 364 consecutive cases, no such complication appeared. This, we believe, is because every reduced fracture was completely reduced and was carefully observed for twenty-four to forty-eight hours after reduction, except as previously noted in olecranon fractures. Open reductions, when necessary, should be done in transcondylar and supracondylar fractures over the lateral epicondyle; the hematoma should be evacuated, the bones aligned, and the limb put up in hyperflexion. With the incision recommended by Jones,[12] we have had no experience. One case of temporary ulnar-nerve palsy occurred in an old fracture of the medial condyle of the humerus treated outside the hospital for one month. One of these fractures occurred in a hemophiliac, and another in a case of erythroblastic anemia. In 2 cases, pressure sores under plaster-of-Paris fixation occurred, and both subsequently healed.

Summary and Conclusions

The incidence of fractures of the forearm and elbow in children under twelve is high.

Careful closed manipulative reduction should be carried out in the treatment of these cases, and if unsatisfactory position and alignment have been obtained, open reduction should be resorted to within forty-eight hours. The incidence of open reduction in this series was 1 per cent in fractures of the distal forearm fractures, none in fractures of the proximal two thirds of the forearm and 6 per cent in fractures of the elbow.

Methods and position of fixation after reduction and the convalescent care are discussed.

The end results in cases adequately followed up give a very clear-cut indication that these fractures, when treated carefully and completely, even those involving the elbow, give a good result in better than 94 per cent of the cases.

There was no case of Volkmann's ischemic contracture in this series.

The authors are indebted to Dr. Frank R. Ober for permission to include cases from the Orthopedic Service in this analysis.

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Discussion

Dr. John F. Gile (Hanover): I think Dr. Thorndike has been particularly fortunate in not having to do more open reductions in such a large series of cases. I am sorry to say that I have had to put in hardware, in probably a smaller series of cases than his. But I believe exactly as he does that if one can manipulate these fractures early and hold them satisfactorily, one will get good results. On the other hand, there will be a certain number of cases, not only in elbow fractures, but also in certain shaft fractures, in which one will have to do something in the way of an open reduction.

Dr. Thorndike (closing): I am surprised that I did not stimulate discussion of a controversial point. I tried to, but you spared me a good deal of argument by your silence. However, I do believe that the important thing, if one has to operate on these fractures, is to do it within forty-eight hours. One cannot mend an elbow fracture satisfactorily after it has united.

THE MEASURE OF A PHYSICIAN'S GREATNESS*

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I HAVE long looked forward to this opportunity of coming back to Tufts and talking to the student body, and I realize that the privilege of delivering a George W. Gay Lecture is no small honor, but on the contrary, one of considerable responsibility. And so, I ask you to spend the time allotted to this lecture in considering with me certain fundamental attributes of medical life that I believe contribute to making one a better physician.

Medicine today, or more particularly the practice of medicine, is so much in the public view that we are indeed in great need of getting ourselves straightened out in these matters. I can assure you that there are scores of scenario writers in Hollywood who could write this address with less travail than I, and with more apparent authority.

Think for a moment, if you will, of my title, "The Measure of a Physician's Greatness," and then reflect how convinced the public is that they have seen or read all the inside of this "being a doctor." Consider with me the dozens and dozens of best sellers that head the week-to-week book lists; notice the lights over your neighborhood motion-picture theater with "Men in White," "Louis Pasteur" and "The Citadel"; listen to your favorite radio program and miss if you can the "Call for Dr. Brent," as the hospital loud-speaker operator opens the radio serial that is current at the moment. Do not for a moment think that the American public have not been backstage in this business of being a physician.

Imagine my amazement, not so many months ago, to see advertised in a Boston paper, with big headlines, "Dr. Christian," only to read further and learn that it was not the distinguished Hersey Professor of Medicine emeritus, but just another radio program. I therefore say to you, conversant as you are with these contemporaneous affairs, that it takes a fair amount of courage to talk to you on such a subject as my title suggests.

Presently, many of you will be graduating into the medical profession at a time of almost unparalleled world unrest. I share with you your bewilderment and lack of understanding about just what the future holds for us as individual physicians and for the profession as a whole, but God be pleased, it will not be a totalitarian future. Nevertheless, it is probably true that the future of medicine will not be entirely under our control. There are grave dangers that the aim of the Government for the complete socialization of the practice of medicine leads in the wrong direction. We have only to look at Germany to see in what direction complete cultural and spiritual control of a nation leads. Even if inspired by the sincerest motives, these efforts must not succeed.

It is on the physician-to-patient relation that the great medical tradition rests. The position we occupy in America today as members of a great profession, whether you view it from a purely scientific angle or from a combination of social and scientific aspects, has never previously been attained. Certainly there have been persons of outstanding genius in every generation, and we, as well as the public in general, have generously paid them homage, but I venture to risk the unqualified statement that you, my friends, are entering medicine in its Golden Age. Therefore, I do not hesitate to go on and tell you what my ideas are of the things that contribute to this agreeable state of affairs.

On the whole, medical students of Tufts have little reason to complain that they are excessively burdened by preaching. Except for an occasional word of advice or direction in the course of a formal lecture or at the introduction of a course or subject, it is from the whole environment of the school that enthusiasm and encouragement flow. It will be in the later months of your medical-school career, when your time is more generally spent in intimate association with sick people at ward rounds and in clinics, that you will profit most, by directly observing the virtues of diligence, kindness and truthfulness in your teachers.

But I must not forget that I am addressing myself to the fundamental attributes that are the basis of a physician's greatness, and I should therefore like to pause for a moment and ask you to consider the very dignity inherent in the title, "physician." Most of you are too young to have known the old-time doctor who was more than a prophet in his community. To many he was the law itself, to others a father confessor. To most of you his attainment of scientific knowledge would seem

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very meager, but in self-sacrifice, nobility of character and wisdom he was in truth a giant.

If I could bring home to you in this dissertation only one sustaining inspiration, it would be the cultivation of the broad understanding that characterized those benevolent family doctors. I am sure, by and large, they never thought in terms of an ethical code, but rather lived their private, as well as their professional, lives in an honorable relation to fellow practitioners and patients. Consequently, the thought that is uppermost in my mind in dealing with medical ethics is, somehow or other, to get you to think of the code, not as a set of rules and regulations, like the by-laws of a state medical society, but rather as professional ideals of duty and obligation.

You will learn, when you get time to indulge yourself in the luxury of reading medical history, that medical ethics go back to the year 2250 B.C. when a Semitic king, Hammurabi, in Babylon, chiseled out a code of ethics on stone tablets. You will often be reminded of the Oath of Hippocrates, which for 2400 years has been the pledge of physicians. How else can we explain the virility of these principles and precepts, which are self-imposed, except by saying that they are based on truth? And may I now remind you that you will soon enter the portals of a profession that has unswervingly adhered to its nobility of purpose since the very beginning of its existence?

I think it would be well to take the time to quote this oath. You may be familiar with it, although I cannot recall having heard it until the day of graduation, and I think the wise and prudent, though departed, Dr. George W. Gay, who sponsored this lecture, expects it. Let me read it to you.

> I swear by Apollo, the Physician, by Aesculapius and Health, and All-heal, and all the gods and goddesses, that, according to my ability and judgment, I will keep this oath and stipulation, — to reckon him who taught me this art equally dear to me as my parents, to share my substance with him and relieve his necessities if required; to regard his offsprings as on the same footing with my own brothers and to teach them this art if they should wish to learn it without fee or stipulation; and that by precept, lecture and every other mode of instruction I will impart a knowledge of the art to my own sons and to those of my teachers and to disciples bound by a stipulation and oath according to the law of medicine, but to none other.
>
> I will follow that method of treatment which according to my ability and judgment I consider for the benefit of my patients and abstain from whatever is deleterious and mischievous. I will give no deadly medicine to anyone if asked, nor suggest any such counsel, furthermore I will not give a woman an instrument to produce abortion. With purity and with holiness I will pass my life and practice my art. I will not cut a person who is suffering with a stone but will leave this to be done by practitioners of this work. Into whatever houses I enter I will go into them for the benefit of the sick and will abstain from every voluntary act of mischief and corruption and further from the seduction of females or males bond or free.
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> Whatever in connection with my medical practice or not in connection with it I may see or hear in the lives of men which ought not be spoken abroad, I will not divulge as reckoning that all such should be kept secret. While I continue to keep this oath unviolated may it be granted to me to enjoy life and the practice of the art respected by all men at all times, but should I trespass and violate this oath may the reverse be my lot.

Certainly these are broad principles of moral conduct from the greatest physician of ancient Greece, and you will do well, in your early days of practice, when unwanted leisure may tempt you to much profitless reading, to study his life and writings. I shall not burden you with many references but would recall that he was the first actually to differentiate diseases and by accurate observation and study to divorce sickness from superstition.

Coming down somewhat closer to our time, you will find a book published in 1803 and written by Dr. Thomas Percival to be most eloquent. This is entitled *Medical Ethics: A code of institutions and precepts adopted to the professional conduct of physicians and surgeons.* From this delightful book, which I recommend to you, is derived the code of ethics of the American Medical Association.

Carefully weighing these many admonitions laid down for us in the code and in the great writings of the master minds of medical history, we find constantly re-emphasized the physician-patient relation and the ever-present reminder that our first duty is to our patients. Certainly, you have a duty to other members of the profession, to the public in general and to yourself. Of these, I shall also have something to say presently, but they naturally follow the other in the order of their importance.

Somewhere in my early medical days, — just when or where, I cannot be sure, but probably from Dr. William H. Robey, whose kindly wisdom, advice and guidance, and example did much toward shaping my own career, — I learned that the treatment of a disease is wholly impersonal but that the treatment of a patient is entirely personal, and that a great physician combines in himself the utmost in scientific knowledge and the quality of complete self-sacrifice. Not so long ago I had the pleasure of discussing some of these qualities with Dr. Soma Weiss, who gave it as

his opinion that the basic elements of greatness were "sincerity and genuine sympathy."

Here I need not dwell on your broad training in the medical sciences, which has been well attended to, but I have found in my years of contact with interns that there is often a sad lack of training in the virtues of tolerance, patience and sincerity. The old notion that physicians are born has almost disappeared. They are not born; they are trained, and they are trained for the care of the sick. The attribute of a self-sacrificing desire to restore health as completely and as quickly as possible has characterized all the great doctors of history, even down to this very day, and when you receive your degree in medicine there goes with it this responsibility to the sick.

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Not all of you will have the two important prerequisites for greatness in the same proportion. With some it will be more science and with others more art. Accordingly, I should not say that with science alone you cannot be great, for there may be those among you who will go into fields of research and pure scientific investigation, those whose careers completely separate them from the care of the sick, those whose names may shine as brilliantly as that of the late Dr. Frederick G. Banting, who gave us insulin for diabetes. But I most sincerely assure you who will be practitioners that the measure of your success depends ultimately on with what measure of both these components you are blessed.

I suppose one of the most puzzling questions that you as young practitioners will ever ask yourselves will be, How do people pick out a particular physician? or How did so-and-so ever happen to call me? I have no clear-cut answer for these questions. I have long thought about this and tried to evaluate the various elements involved. Salesmanship — and I mean the ability to sell yourself — seems very important. Personality, in the sense of the sum total of character, must be equally important, although I am sure that ability and skill may, sooner than you would believe, become the determining factors.

Probably your first actual responsibility to a sick person will come in the hospital wards, and a problem that has often come to my mind of late has to do with your handling of patients as house officers, during either your internship or residency. Here I admonish you not to say things, publicly or in the hearing of others, that will hurt the feelings of your patients or frighten them, for it serves no good purpose other than to mark you as lacking in kindliness and sympathy.

Because of their teaching value, clinics and ward rounds have become very general, even in the small hospitals widely separated from medical schools. If carefully considered, they can be conducted without emotional damage to the patient, although not always, I fear.

I had a recent experience in a large metropolitan teaching hospital that makes this point clear. I was there for a brief visit with the chief in medicine, one of our greatest present-day internists; he turned me over for a short ward round with one of the younger members of his teaching staff, who appeared to be very familiar with his cases and well informed medically. However, he talked freely and openly. It was not a large ward, and everyone in the place knew the most intimate details of the other's histories, both medical and social, except for that of one timid woman of about fifty-five. She was in the next to the last bed, and when we came up to it, the intern gave me her clinical record and pointed to the x-ray report, which showed extensive cancer of the stomach. He said not one word about the case and continued on to the last patient, but his silence was infinitely more eloquent than his previous discussion of the other cases. As he put the record back on the foot of the bed and was about to go on, the poor woman broke into tears and cried out, "Oh, I am sure I have some terrible disease because you always tell about the others and then whisper about me." It was no easy job for this physician and myself to quiet her down, and I am sure that we did not begin to undo the damage my visit had caused.

Lest you think that this question of the patients' emotional reactions to their exhibitions on rounds and at clinics is one of very minor importance, I might tell you that at this time, in more than one of our major teaching centers, a very serious study of just this problem is being made.

The matter of consultations should find a place in the early part of this presentation because you will not be long in practice before you will come face to face with this aspect of medical life. You will find a great divergence of opinion among your confreres on the subject, and I can serve you best by presenting it from a personal point of view.

As your years in practice increase, you will most surely fall into one or the other of two general groups: those who seek and desire consultations, and those who spurn and abhor them. It is my counsel that you be in the first group. Confronted with a serious situation, do not risk carrying the entire responsibility; share it with some consultant, preferably one of your own choice. Ask for the

consultation early in the illness, for should you delay and have the suggestion come from the family they will most certainly insist on their own choice rather than yours, and you will be at some disadvantage, for this circumstance is usually quite obvious to the consultant.

In general, it is a good plan never to object when a patient's family asks for a consultation. You may take the position that it is superfluous and a waste of money, but the knowledge that they have given their loved one this special attention often means comfort and satisfaction to a family. Put yourself in the position of a devoted son whose mother may be dying of a surely fatal chronic ailment: he wants to give his mother all he can afford, and he may get great help in his grief just by knowing that nothing was left undone in her last illness.

When you suggest and choose the consultant, it is infinitely more satisfactory, since invariably you will pick an older man with standing and authority whose years of experience with similar cases will be, at least in some measure, helpful and whose attitude toward you will be one of courtesy and respect. Share with him the responsibility in a serious case; his recognized reputation can better stand the strain of a fatal outcome than yours, particularly in your early years. More than a few physicians of my acquaintance have been handicapped because such an unfortunate circumstance occurred when they were first starting in practice.

Often enough, if you interpose an objection to a consultation, you will find the patient or family losing faith and entertaining a suspicion that you are not entirely sure of yourself. Invariably this leads to a change of doctors and to an undeserved feeling of ill will on both sides. When you are a seasoned practitioner, you will know how to handle each individual case, but in those early, hopeful years give both the patient and yourself the benefit of any doubt.

There is the specific situation, to be sure, in which the "in-laws" want their own physician in consultation, and not so long ago it was my privilege to straighten out just such an awkward situation for a young physician. I met him outside the house, listened to his complaints about the family, and counseled him out of my own experience. He was entirely right about the case, and I frankly said so to the wife's family. He was a good doctor and immediately recognized the value of just that sort of co-operation. Since then I doubt if a month goes by that he does not call me in on some case. Usually, even if your case is not serious, you will learn something from such a conference, particularly if you pick the consultant yourself.

Here might be appended a word of advice about the grievous sin of magnifying the seriousness of cases so that your skill in relieving them might have more importance. If you subscribe to the attribute of sincerity, you will never be guilty of this; nor will you consciously minimize the gravity of a case to the family, for this serves no good purpose and convinces them that you did not understand the case. Tell the family the true facts of the matter as you see them. It may be and, in fact, often is better for the patient not to know when he has a fatal illness; let him go on hoping, contented in his confidence that you will rescue him. There are many exceptions, however, and you cannot make it a universal rule. You will meet a patient occasionally who wants to be told, and should be told, the complete truth of his condition and chance of recovery. Such patients often accept a fatal prognosis with great fortitude and resignation, particularly if they have strong religious convictions, and spend their remaining days in spiritual contemplation and expectation.

When I come to a discussion of your duty to other members of the profession, I am really treading on sacred ground, because it is here that you are most apt, in your younger days, to stub your toes and unwittingly offend a fellow practitioner. You will hear repeatedly of professional courtesy in this regard, but it is much more than this, when you meditate on it — more perhaps like the spirit of the medieval guilds, in which the interest of each member was subservient to the main interests of the group. You will find in the membership of your local and state medical societies, as well as in the specialty organizations, the best expression of this guild spirit: a genuine friendliness and unselfish willingness to share each other's special knowledge and attainments.

That there is great need for this organized strength in our day, when we are threatened on so many sides, is readily conceded by all physicians, for there are many economic and business phases to the medical guild that require organization, and many inroads from the cults or restrictions from the legislature that must be contended with. Yet, it is to the intellectual and cultural part of your association that you will probably give most interest, for I have known physicians who, through circumstances not of their own making or at least beyond their own control, deprived of these opportunities of frequent exchange of professional ideas, confess to much unhappiness.

In good time it may become your privilege to

be known to your patients as the "beloved doctor," and a gratifying state of affairs this is, but there is nothing you can hope for from your medical life half so precious as the respect and affection of your colleagues.

As your years increase, you will find more and more that you are called to treat fellow physicians and their families. Here, indeed, is an attribute of greatness, and when you get to be known as the "doctor's doctor," you will know of what I speak. Be sure and give the very best of yourself, particularly to physicians' widows and children. You will not be offered a fee for this service, but it furnishes the best expression of that spirit of the guild of which I have previously spoken.

A thing that will trouble you often, as time goes on, is the awkward situation of being called into a case that another physician has been attending. The handling of this predicament takes great tact, and each case different handling. It matters little who the doctor is or how great his limitations of medical knowledge; be fair and even generous to him, and I beseech you not to indulge in detraction. To my way of thinking, detraction is the cardinal sin of the medical profession. It is so easy in the intimate relation of the sickroom or office to build yourself up at the expense of the former doctor. Suppose he did miss a diagnosis that seems easy to you. Usually, there are new signs and symptoms that have helped you, but at least in all humility think of the ones you must have missed.

For the last twenty years or more, I have had knowledge of practically every medical and dental malpractice suit that has been started in my state, both as the examiner for insurance companies and as chairman of the local and State committees concerned with such cases. I can assure you that in more than half the actions threatened or actually brought a thoughtless detraction, or even a malicious detraction, by a fellow practitioner was the starting point of the trouble.

Make it a rule, when somebody at the club asks you what you think of Dr. So-and-So, to be charitable, no matter what your private opinion is. And beware of any lawyer who buttonholes you on the street corner and details a hypothetical case that has had a bad end result. The chances are he has a prospective malpractice case. Watch carefully about getting into any case in which the previous doctor has not been discharged. If there is to be a change, the patient or family must make it, and the other physicians must be notified by the family, not by you. Going into cases without making certain of this fact is grievously unethical. There is no reason why a patient should not change doctors if he wishes, and the practice is very common with certain races and types. In this age of rapid change, when people move from one house to another or from one section of a city to another, a physician cannot expect them all to stay with him forever. So far as my observation goes, this is precisely the way all young physicians develop a practice, and often in these days of widely disseminated medical knowledge, people believe that a young doctor has newer and more up-to-date ideas.

However, a situation that has caused plenty of trouble for young physicians arises when another doctor asks them to cover his practice while he is out of town or on a vacation, whether for a day, a week or a much longer time. Sometimes it is just an emergency that he cannot get to, or perhaps he cannot be reached. Whichever of these circumstances prevails, make no more visits than are absolutely needed. In the first, immediately turn the case back to him when he resumes practice, and should it be an emergency call, get him on the telephone as soon as is reasonable and tell him what you found and what you prescribed or advised. Very frequently you will be urged by the family, in either situation, to remain on the case. You will not do this I am sure, because it is strictly unethical; if you do, you will soon have a reputation for deliberately stealing cases that will be difficult to live down. This is a very common source of friction among physicians, and I could cite specific cases in which promising young doctors got reputations for this very early in practice, with disastrous results for their future.

In good time, you will get to know some of these unhappy persons who make up the fringe of respectable medicine, many of them with great capacity and no little skill, but lacking that finer moral quality that would have made them great. The cultists you need not concern yourself with, for they are not your colleagues, and in this section of the country we do not invite or accept them in our medical societies. We do not consult with them professionally, and you have no ethical duty to them beyond that of pure social ethics.

The matter of fees seems an overemphasized feature of such talks as this. Perhaps it takes care of itself better now than in former generations, for you will rarely be overpaid; on the contrary you will frequently be underpaid or perhaps not paid at all. Should you embark on

general practice, you will most probably find the office and house fee a well-settled local custom, long before your arrival. In the special fields, this is also true, although in surgery the situation is more flexible. The honorable surgeon will set a fee somewhat according to the patient's means, and this is equally true of consultations. Often it is my custom to ask the doctor who calls me about the family circumstances and even to let him suggest the fee. I do not feel too strongly about this plan, however, for often he sets too low a valuation on the consultation, and experience will teach you that many people value your services at just the price you put on them. Contrasted to this, however, you will find among your true charity cases and your free-ward cases in the hospital those who set a value, much beyond price, on what you do for them. It is an open question to what extent a large income elevates a professional man and to what extent a generally high level of income elevates the whole profession. Material prosperity should be valued in its proper perspective.

Now let me turn from this consideration of duty to your patients and duty to your professional brothers to that of the public in its larger sense. It is not in my mind to discuss public service as it applies to a health officer, a medical officer of the United States Army or Navy or an official of a corporate or tax-supported institution or government department, but specifically, to dwell for a few moments on another aspect of the life of the practitioner.

In alluding to some of these, it might be well to dispose first of a question often raised by the laity and to some extent believed by them, namely, Is a physician legally obliged to respond to a professional call from anyone? If the call comes from complete strangers, or from those whom you never previously attended for an illness that might be linked to this call, it may be unreservedly stated that you have no responsibility to accept such a case. But should you choose to go in response to such a summons and engage in the case, you do acquire a legal responsibility, for you have become a party to an implied, even though unwritten, contract, and you will be subject under all the laws and statutes applicable to contracts, even to defending yourself in a court of law for any breech thereof. This being so, there remains, nevertheless, the certainty that the true physician has ever been ready and willing to respond in an emergency, for it is quite obvious that any physician would be more helpful than a lay person, even those who have for years limited their practice and studies to a special branch. Such a situation was my experience a few years ago when I came on the scene of an automobile accident and found the person who was adjusting a pillow and side splint to a fractured lower leg to be the senior eye specialist of our hospital; in talking it over with me later, he told me what a pleasure he got out of doing it, although I am sure he never learned the victim's name, much less got a fee for his trouble.

Another duty to the public on which I am inclined to dwell somewhat, is one, if you will permit me to say so, with which I have had considerable experience. It is your appearing before courts of law and boards of adjudication. This is a duty that you cannot hope to escape, for on a day when it seems that nothing more can be heaped on you in the way of other people's troubles, there will come into your consulting room a large and rather sober-looking man. Just as you are about to offer him your comfortable desk-side chair and ask him his name for your clinical record, he will reach into an inside pocket and produce, like a rabbit out of a hat, a court summons demanding your appearance in court at 9 a.m. the next day. This hour, curiously enough, will be the very time you had reserved at the hospital for a tonsillectomy.

Few of you who are going into general practice, or even the specialties, will have quite enough of this to give you a feeling of being at home on the witness stand, and since it is a matter of some importance to your pride that you acquit yourself with credit, both personally and professionally, I venture this concise advice: be scrupulous in your honesty. No doctor on the witness stand who keeps this in mind is ever in trouble, although I concede the difficulty of not being biased, either for your patient or for the insurance company that employs you. To this might be added the desirability of keeping your answers as simple as the purport of the query permits, the uselessness of volunteering information not asked for and, finally, the value of preparing yourself for testifying by familiarizing yourself with the factors involved, as they relate to medicine in general and the case in particular. It matters little how clever and menacing the cross-examiner; he is a lawyer, and although he may have a well-deserved legal reputation and a large medical vocabulary, you are a physician, skilled in the field about which you are testifying, not deviating from the known facts, and not afraid to say, "I don't know."

It was my good fortune very early in my medical life to have had a word of advice on this matter from Dr. Timothy Leary. While I was a house officer at the Boston City Hospital, an unconscious patient was admitted who obviously was

dying of meningitis. A lumbar puncture proved it to be a pneumococcal meningitis. We had no serum or sulfathiazole in those days, and the patient died in a few hours. It so happened that the patient had been in a street fight the previous day, and on this basis it became a medicolegal death; Dr. Leary, who was the medical examiner, autopsied the man and found a skull fracture through the temporal bone and the probable point of entry for the pneumococci. The other details are unimportant, but there was a political angle to the case, and it finally developed into a charge of manslaughter. Presently I was summoned into court; this was my first experience, and you may rightly suspect that I was nervous, because my testimony was important in linking this death with Dr. Leary's findings. When I met Dr. Leary in the corridor of the courthouse, I told him how nervous I was and asked him what advice he could give me, since it was my first appearance in court as a witness. His counsel I pass on to you: "Tell the truth and don't deviate from it, no matter what they ask you. If you don't know, say so; don't quibble and don't split hairs."

It is probable that in the course of your practice, you will often be called on for health certificates, disability statements and compensation forms, and, at the moment, there are those who seek a statement that they have a disability that will exempt them from military training. Surely by now, there is nothing for me to add in this regard, for your self-imposed rule of conduct in all your dealings with your fellows will be the guide.

It may be that I should add a word or two about advertising, which, I believe, is in much the same position as fee splitting. In New England it just is not done, or if it is, it has quite escaped my observation. You may occasionally need a modest and dignified notice in the local paper on your return to practice following a reasonably long absence, and this is quite proper; but conscious and deliberate advertising should be generously left to the cultists and quacks.

Publicity seeking, however, is quite a different matter and a much more insidious disease. In calling your attention to it, let it be assumed that you recognize I allude to the pursuit of this siren, who may well lure you from your high purpose to the rocks of mediocrity. Your measure of greatness may well be the relative rarity with which your name appears in the daily press and the frequency of its appearance in the *Quarterly Cumulative Index*. In no sense does this statement imply that when you have reached a position of prominence and importance in your community you will demand anonymity; rather, it is my hope that it will suggest which of these two points of view has in it attributes of greatness. You will be expected, from time to time, to lend the authority of your name to a radio talk, which, when properly sponsored, is completely ethical; in fact, it might rightfully be considered among your duties to the public, for we are the ones to educate laymen in matters that pertain to their health. It is a vast and tremendously interested audience that listens to physicians on the radio. If kept within proper limitations, this activity does much to counteract the mischief of the cults.

Passing from these responsibilities to the public, consider with me the more intimate and personal aspects of medical life, which I have chosen to call "duties to yourself." The public will demand much of you, organized medicine its share, and your patients practically all of you; therefore, it is to those things that contrast you with others of our profession, also serving this triad of taskmasters, that I shall turn my attention.

I might enumerate a long list of "don't's," such as dressing flashily, driving around in a bright-red automobile and not keeping your person and office businesslike, but I incline to the general belief that you are well informed on these matters from your own observation and general knowledge. Furthermore, I do not intend to spend much time in stressing the importance that attaches to the possession of a good professional manner. This you will acquire in just the right proportion, as you respect the dignity of your calling. Perhaps the Vandyke beard and the Prince Albert coat did enhance the professional air of those doctors of a former generation. However, I think you need not worry about acquiring a silk hat as a badge of your profession, lest your patients think that you have just dropped in on your way to a wedding or a funeral.

My concern is more with your acquiring a continuing medical capacity. You have, by now, become aware of the inescapable fact that medical knowledge is never static, that many times you must unlearn and relearn the management of a given disease, in the light of new information and discoveries. If you review the papers written on diabetes by such an authority as Dr. Elliott P. Joslin, in the space of his professional experience, you will see the truth of this statement.

Presently many of you will be starting or seeking internships. In my medical-school days only a part of the graduates took intern training. I

think a large majority of the class did, but it was in no sense required. In your day, it is required for licensure in many states. This is a wise policy, as those of us who have served on state examining boards know, for in reality a year of internship is a fifth medical-school year and is most essential. For the reason that many graduates went directly into general practice from school in those days, we learned much in the fourth year that you will meet for the first time in your internship.

What it is that makes this internship experience so stimulating is not easily explained. Some of the elements are quite obvious: for example, your first responsibility in the actual treatment of disease; other elements are intangible, but the sum total of all makes this one of the happiest periods of your entire life. Many believe that the internship is the focal point in the medical career. It is here that you will find the guidance and preceptorship that are necessarily lacking in the impersonal atmosphere of the medical school. It is here that you will begin to visualize your future. If you are a clear thinker, you will discover where your talents lie, and you will zealously foster them. Some among you will find it possible to go beyond this internship, to the residencies or fellowships that are increasingly available.

Those of you who are going into general practice or who because of economic limitations find it impossible to continue your training period should not be dismayed, for there are abundant opportunities for short postgraduate and refresher courses. It would not be fair in these troubled days if I did not make some reference to the probability of your being called for a year of military training. It is not too early for me to predict that you will derive great benefit from this. With a commission of first lieutenant, you will have a certain amount of financial security, and you are likely to have considerably more leisure than you had during your internship.

With the expansion of the medical departments of the United States Army and Navy, under the enlightened guidance of the hierarchy of the Services, I should hazard the opinion that this will probably become the greatest postgraduate medical school of all times. The possibility exists that during the so-called "training period," if you are fortunate enough to be in one of the tremendous thousand-bed or two-thousand-bed hospitals of the training centers, you may discover for yourself an aptitude for one of the special branches of practice. Beyond a doubt, opportunity will be afforded in these large centers for intensive specialized training, and I should not be surprised if recognition of this training by the boards of certification in these specialties would naturally follow. Should the misfortune of our entry into the war occur, I am not prophet enough to say what the situation is likely to be.

When your hospital days are nearing their close, one of the greatest problems for many of you will be deciding where you will open an office. There is but one bit of general advice in this regard that has the slightest value to you: start practice where you want to live your life out and where you will be happy.

I can promise you that in your first few months many of you will be utterly convinced that you have made a complete mistake and that any one of the other places you considered was the right one. Some of you will spend many hours wrestling with this problem. Older physicians and staff members may give you excellent advice in arriving at a decision, and although it may not be universally unbiased, it is, in my opinion, likely to be genuinely helpful.

Occasionally, a young physician makes a mistake in picking the location in which to start practice. This can easily be corrected, but the mistake should not be often repeated. There is little advantage to any doctor in frequent changes of location, although some seem never to take root, and move on from place to place. A danger in this is that you may be suspected of not paying your bills, and you will find that those who repeatedly change their locations are rarely successful. This does not mean, however, that you who start in the poorer sections of cities should not move to the Back Bay of your chosen community. On the contrary, this is just what you should do, in my opinion. Despite this, I have occasionally known a truly great physician who began his practice on the "other side of the railroad track," and then, through sheer loyalty to his practice among these less fortunate people, lived out his professional cycle in their midst. This devotion and self-sacrifice to an ideal of service, this willingness to forego the pretentious office and home, may well have been the measure of his greatness.

As an example of the importance of this matter of picking the proper location I shall cite a case. This physician was truly great, judged by all these stipulations I am suggesting to you, but he, of all the physicians of my acquaintance, was the most unhappy. His background was one of culture and refinement; his father, a successful physician with a large city practice, died while he was still in college, and except for this unfortunate circumstance, my friend undoubtedly would have

become an outstanding practitioner in the large Pennsylvania city where his father had lived. After an internship that was completed with credit to himself, he was advised by his father's closest friend, a distinguished surgeon of Boston, to go to one of the islands off the Massachusetts coast, and take the practice left by an elderly gentleman recently deceased. This surgeon adviser knew the local conditions on the island, since he had a summer place there, and was a frequent visitor, and it was in his mind that his friend's son might find here a temporary and somewhat lucrative ready-made practice, which would give him some badly needed funds with which he might open an office in a permanent location. Many events conspired to alter these plans; a severe attack of typhoid fever the following fall kept him there through the winter, and then a chain of other circumstances kept him on indefinitely. Always the mirage of going back to a big center was just another summer away, but then there was this case and that case that he could not abandon. There was the problem of the local bank, of which he was by then president, and the cottage hospital for which he had worked so unceasingly. More and more as these chains bound him to the island he grew to hate it all.

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Where was this friendly professional intercourse he had always looked forward to? Where was he to find the intellectual companionship that was his right and due? Certainly not with the poor island fishermen, and certainly not with the summer colonists, who were his bread and butter, but with whom he was too busy and too tired to do more than treat their neuroses or operate on their emergency abdomens. And, by way of parenthesis, he could do a creditable laparotomy or a mastoid operation, if the need arose and no specialist was available.

I visited with him occasionally when I could afford a brief holiday, and his enthusiasm, clarity and insight in discussing his problem cases were always inspiring. On my last visit with him, just before going to Europe during World War I, we tried to figure out some plan of getting him into military service. He would have loved it, had it been possible, because he was a great American as well as a great physician. But they turned him down; he was too old for service, and thus the island held him. He has been dead some years, following an operation in a Boston hospital, and I sometimes wonder, if we could sit down again for another of our medical chats, if he would not say, "Well, you know, I did escape; I died on the mainland."

I am quite aware that somewhere along about here you should be told to shun alcohol, or words to that effect. Permit me to say that to those of you who entertain any aspiration of greatness as physicians there will be clear understanding on this point. For the occasional physician of your time who believes he can combine the practice of medicine with public or excessive drinking, any words of mine would be wasted. For him I bespeak your kindness and consideration, since he is to be looked on as an unfortunate, as one who must have possessed qualifications that entitled him to admission among you, but who is sadly lacking in the qualities we have been discussing.

Among the several other things to be briefly mentioned are a regard for your investments. It will strike you as ridiculous if, in these days of professional investment counselors, another laborer in the vineyard tells you to buy annuities rather than common stocks. The only investment I could be sure enough of to recommend to you, in the expectation of its paying dividends, is a greater love and knowledge of your profession. This will build you a heritage that you will be proud to bequeath to yet another generation of physicians.

Again, this business of recreation and vacation generally seems to take care of itself. In later years you will be hearing much about "all work and no play." For some physicians it might be reversed to "all play and no work." In other walks of life this problem is much the same as in ours. You will often be called on to advise patients in this matter, and the provident physician will wisely apply these sensible recommendations to his own needs. And while I am on this topic, hobbies should not fail of some notice. From personal experience I can suggest none, for, although I believe that a hobby should be something completely divorced from one's usual occupation, my own seems to be going to medical meetings.

Finally, in concluding this very inadequate presentation of a lecture that has so often in the past and will surely in the future be more eloquently delivered and more logically conceived, I have these last words to say. Physicians for the most part are gentlemen, and conduct their public and private lives as such. My counsel may be a counsel of perfection, in many respects, rarely attained perhaps, yet offering you respect and affection from your patients, an exalted place in the public mind, honors from your colleagues and the interior satisfaction that comes of a useful and happy life. It is in these attributes that I believe you will find the measure of your greatness.

221 Thayer Street

DISSECTING ANEURYSM OF THE AORTA

Report of a Case

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DISSECTING aneurysm of the aorta was first described more than two hundred years ago by a British physician named Nicholls,[1] who demonstrated in 1728 that rupture of the inner coat of the aorta could occur without rupture of the outer coat, an aneurysm developing within the middle layer. The same physician in 1761 performed an autopsy on the body of King George II, of England, who had died suddenly while straining at stool. Nicholls found a dissecting aneurysm of the aorta, which by pressure on the pulmonary artery had caused rupture of the right ventricle and sudden death. The great anatomist, Morgagni,[2] recognized dissecting aneurysms and described an autopsied case as early as 1769. A striking account of a dissecting aneurysm occurring during labor was reported by Lynn[3] in 1798. The master French clinician, Laënnec,[4] was familiar with this condition, to which he applied the term, "aneurysma dissecans," in 1819. The first correct ante-mortem diagnosis was made in 1856 by Swaine.[5]

Although 500 cases of rupture of the aorta appeared in the literature during the next eighty years, in only 9 was a correct ante-mortem diagnosis made until the subject was carefully reviewed by Osgood et al.,[6] and by Peery[7] in 1936 and independently studied a year later by McGeachy and Paullin,[8] who reported 3 cases of their own, with correct diagnosis before death. As a result of these recent analytic clinical studies, interest in the condition has received renewed impetus during the last three or four years, and reports of accurate ante-mortem diagnoses are no longer a rarity. However, since dissecting aneurysm of the aorta is found with increasing frequency and since this condition may be readily confused with coronary thrombosis, we believe that a short outline of the clinical features of dissecting aortic aneurysm, with an illustrative case diagnosed on the first day of the disease, will not be amiss.

The clinical picture may be confusing because of the severity of the onset, which may make a detailed examination impossible, and because of the rapid sequence of alarming symptoms, which spell a fatal termination in twenty-four hours or less in more than 75 per cent of the patients. Sudden death is almost a common denominator and often occurs before diagnosis can be made. More recently, a chronic form of the disease, presenting symptoms of progressive decompensation simulating cardiovascular syphilis, has been recognized. In 4 such cases reported by Gouley and Anderson,[9] the patients did not complain of any pain whatever during the entire course of their disease, which varied in duration from two months to four years.

A dissecting aneurysm develops as a result of the rupture of the intimal lining of the aorta a short distance above the valve ring, either at the site of an arteriosclerotic plaque[7] or at the locus of rupture of one of the vasa vasorum.[10] In either event, the lesion is associated with arteriosclerotic or cystic changes in the elastic tissue of the media (necrosis media aortica cystica).[11] Degeneration of the media, possibly owing to metabolic toxins, leads to intramural changes and thus paves the way for dissection by the aneurysm.[12] This condition is not limited to the aorta alone, since it is primarily a disease of blood vessels with elastic tissue and may therefore appear in the subclavian or iliac arteries, or both. Blood from the lumen is forced through the tear in the intima into the medial coat, where dissection begins at once and progresses very rapidly depending on the height of the systolic pressure and the extent of the cystic degeneration of the elastic tissue in the middle third of the media. The sudden rupture of the intima, with tearing of the medial coat of the aorta, permits the blood to dissect its way between the layers of the media along the entire course of the aorta or outward within the medial coat of the subclavian arteries or downward within the iliac arteries.

This aneurysmal extravasation of blood under high pressure is usually precipitated by emotional excitement or sudden physical exertion. The onset is accompanied by exquisite pain and often by extreme shock, which in itself may be fatal. At first the pain is either thoracic or epigastric, then rapidly spreads downward to the lower abdomen or to the lumbar region and the legs. Vomiting may be associated with the epigastric

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pain, but usually there is little or no abdominal rigidity. As the aneurysm dissects its path between the coats of the aorta, impairment of the circulation to and from the adjacent viscera gives rise to a host of symptoms. Cyanosis and engorgement of the thoracic veins may result from pressure of the aneurysm on these blood vessels. Inefficiency of the cerebral circulation may be noted, owing to involvement of the carotid or innominate arteries. Inequality of the blood pressure may occur in the two arms. Paralysis of the left recurrent laryngeal nerve is not uncommon; dysphagia due to esophageal pressure has been reported. Dyspnea resulting from crowding of the left lung is a fairly frequent finding. Left-sided pleural effusion or collapse of the left lower lobe may occur because of pressure of the aneurysm in this region. Partial occlusion of the renal arteries often gives rise to hematuria, followed by anuria. Further dissection of the aneurysm downward toward the iliac region embarrasses the peripheral circulation in the limbs, as shown by progressive failure of motor power in the lower extremities. The pulsation of the dorsalis-pedis artery may be lost in one or both feet. Blood-pressure readings in the right and left popliteal regions may show wide discrepancies. The legs become cold, cyanotic and flaccid. Gangrene has been reported as a terminal affair, although few patients live long enough to develop this complication. Impairment of the circulation of the lower extremities has been thought to be due to involvement of the lower intercostal and lumbar branches of the aorta to the anterior and posterior spinal vessels, the dissection thus interfering with the circulation of the spinal cord.[13] Inequality of the blood-pressure determinations in the legs may result from constriction of the lumen of the iliac artery as the aneurysm dissects its way within and between the layers of the medial coat.

The initial pain associated with a dissecting aneurysm of the aorta is typically excruciating in character and may be described by the patient as a rending, tearing or rupturing sensation over the precordium, between the scapulas, in the neck, in the epigastrium or in the lumbar region. The pain spreads from the front to the back or vice versa, and usually from the chest to the abdomen and back and down the legs. Rarely does it radiate to the arms. In the atypical form, the "misery" may be mild, indefinite and intermittent, or conspicuous by its absence.[9] On the other hand, the pain may be excruciating in character and entirely localized below the diaphragm, and may thus present the clinical picture of an acute surgical abdomen.[14] But as a rule, a wide, rapidly progressing spread of pain is almost pathognomonic. Shock and collapse are common, and dissecting aneurysm of the aorta is a more frequent cause of sudden death than is generally realized.

TABLE 1. *Differential Diagnosis of Dissecting Aneurysm of the Aorta and Coronary Thrombosis.*

SYMPTOMS AND FINDINGS	DISSECTING ANEURYSM	CORONARY THROMBOSIS
Pain	Sudden, tearing, terrific	Oppression develops slowly.
Occurrence	Exertion usually precipitates initial pain.	May come on while the patient is at rest
Location of pain	High in chest, behind sternum (may be entirely abdominal or referred only to the lower extremities)	Fairly low in the chest
Radiation of pain	To the back in the thoracic or lumbar region	To the neck and left inner arm
Pericardial friction rub	Absent	May appear in a few hours
X-ray findings	Aneurysmal shadow (may extend along a cervical vessel)	Normal mediastinum
Heart	Usually enlarged (previous hypertension)	May be of normal size
Electrocardiography	Inconstant changes (if any)	Characteristic changes
Circulatory block of an extremity	Common, but transient	Uncommon; embolic and permanent.
Central-nervous-system symptoms	Paralysis may be partial and progressive or complete (hemiplegia).	Absent; apprehension often a prominent feature.
Pleural effusion	Fairly frequent	Very rare (except in chronic decompensation)
Vasodilator drugs	No effect	May relieve anginal syndrome

This disease occurs usually after the age of fifty, oftener in men than in women, and is found in patients with high blood pressure and extensive arteriosclerosis. The average frequency of this condition at autopsy is 1 case in 630.[15] In the majority of patients, the blood pressure remains elevated throughout the disease, and the higher the degree of hypertension the more rapidly the aneurysm dissects its way downward along the aorta. The clinical picture often resembles the syndrome of coronary thrombosis, but the sudden and dramatic onset of thoracic pain and the persistent hypertension in the presence of shock should lead one to suspect a dissecting aneurysm of the aorta.[16] The x-ray, fluoroscopic and electrocardiographic findings aid in establishing the diagnosis if the patient is not too ill to submit to these procedures. If the patient is *in extremis*, the correct diagnosis may be most difficult. Indeed, the history alone may be of great value in such cases. When no accurate his-

tory is obtainable, one must consider and rule out pulmonary embolism, spontaneous pneumothorax, ruptured peptic ulcer, cholelithiasis, renal calculus, rupture of a mediastinal abscess and hemorrhage from a new growth in this area. Perforation of a saccular aneurysm and cerebral hemorrhage should not be lightly discarded from the examiner's mind. To clarify the situation, Table 1 presents an outline of the main points of difference between dissecting aneurysm and coronary thrombosis.

The following case illustrates some of these points, since the diagnosis was suspected a few hours after the onset of the initial attack and was confirmed by x-ray films and electrocardiograms later the same day. Post-mortem examination on the nineteenth day of the disease revealed a dissecting aneurysm of the aorta, with death due to rupture of the aneurysm into the left pleural sac.

Case Report

A. P. W., a 63-year-old banker, was suddenly stricken with terrific pain in the chest and back at 11:15 a.m. on March 11, 1940, while sitting at his desk. An emergency call was sent to his physician, who saw him within 5 minutes after the onset of the attack. The patient complained of unbearable substernal pain radiating posteriorly between the scapulas and to the right upper quadrant. He stated that at first the pain struck him in the chest and then rapidly shifted to the back and side. His color was ash gray, and he appeared to be going into a state of shock. He was very restless, and begged to lie down on the floor of his office. The pulse rate was only 48; the blood pressure was not taken at that time because the patient broke out in cold perspiration, lost consciousness, and looked as though he were going to die at once. However, he roused partially and complained bitterly of substernal and subscapular agony.

The patient's father had died of arteriosclerosis at the age of 63; his mother succumbed at 28 years to meningitis. One brother and 2 half-sisters were living and well.

The patient stated that he had always been in good health. It was learned from his wife, however, that at the age of 30, he had been ill for a year with "heart trouble" and that he had had to be "careful" for the rest of his life. The exact nature of this trouble could not be determined, but may have been an endocarditis or aortitis. One of us (C. C. S.) had seen him several times off and on because of minor complaints for the previous 4 or 5 years. At no time within this period was there any evidence of cardiovascular disease or hypertension. The blood Wassermann reaction was negative, and there were no clinical signs or symptoms of syphilis.

The patient was given a perle of amyl nitrite by inhalation and a 1/150-gr. tablet of nitroglycerin under the tongue. Since this produced no relief, ¼ gr. of morphine and 1/100 gr. of atropine were given hypodermically. While the patient was waiting for the ambulance, the pain and shock increased to an alarming degree, and he was therefore given another ¼ gr. of morphine by mouth, but with little effect.

The patient was admitted to the Rockingham Hospital within less than ½ hour after the onset of the attack, with a tentative diagnosis of coronary thrombosis. His condition apeared to be very critical. The unbearable pain in the chest, back, and right upper quadrant still continued, and there was marked cyanosis of the lips and fingernails. The pulse rate was then found to be 56, and the blood pressure 222/70. The patient received 20 cc. of aminophylline solution intravenously, which brought the pulse rate up to 72 but did not relieve the precordial pain.

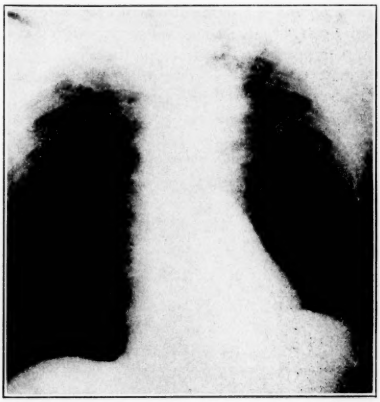

Figure 1. *X-Ray Film of Chest.*

This film, taken with a portable machine on the first day of the disease, shows definite widening of the aortic arch in the region of the transverse and descending aorta.

He was therefore given another ¼ gr. of morphine hypodermically and placed in an oxygen tent. He did not tolerate the tent well because of restlessness, and it was thought best to administer sufficient morphine to control his suffering. At 1:00 p.m., he received a fourth ¼-gr. dose of morphine, which was repeated at 2:45 p.m. In other words, 1¼ gr. of morphine was necessary within 3 hours to quiet the patient. Nitroglycerin, 1/100 gr., was given under the tongue as often as necessary to obtund his pain. The systolic blood pressure, however, failed to fall below 220. The patient appeared to be too ill to submit to physical examination for several hours.

The admission diagnosis of coronary thrombosis was considered untenable because of the extreme severity and continuance of pain in spite of massive doses of morphine and the nitrites. Moreover, the persistent bradycardia and the hypertension in the presence of pronounced shock were very atypical of coronary thrombosis. Because of the general picture, the likelihood of a dissecting aneurysm of the aorta was suggested by his physician (C. C. S.) and the consultant (H. T. F.). This diagnosis was supported by an electrocardiogram, which was negative except for inversion of T_4 and by a roentgenogram (Fig. 1), which showed a probable dilatation of the descending aorta.

Examination of the blood on admission revealed a red-cell count of 4,620,000 with a hemoglobin of 85 per cent, and a white-cell count of 10,100 with 80 per cent polymorphonuclear leukocytes.

The patient ran a septic type of temperature for the 1st week. During this period he was very critically ill,

and the higher his temperature, the graver was his condition. On the 8th, 9th and 10th days of hospital residence, he remained afebrile and showed gradual improvement. From the 12th to 19th days, the fever reappeared, probably owing to further dissection of the aneurysm, and the prognosis became more guarded.

The hypertension present on admission persisted for 2 days. On March 13, the blood pressure reading was within normal limits, 160/84. On March 14, there was a sudden rise of the temperature to 101°F., with extreme back pain and a concomitant fall in the blood pressure to 90/60 as the patient again sank into a state of shock. It was believed that the aneurysm had dissected and torn its way through the aortic hiatus of the diaphragm, because the pain in the region of the mid-back was excruciating. The patient rallied following the administration of stimulants, and the next day presented marked icterus of the skin and scleras.

On March 12, marked dullness on percussion was elicited in the interscapular area on both sides of the spine. Over this region one could hear a faint, low-pitched and continuous roar that was not associated with or affected by the respiratory sounds over the lung hili. Over the course of days, the dullness gradually increased in extent and the bruit in intensity, until both could be heard distinctly from the pulmonary apices to the sacrum over the paravertebral regions. No visible or palpable pulsations were noted posteriorly at any time, and the patient was too sick to be fluoroscoped during his entire illness.

Auricular fibrillation set in on March 13, but responded promptly to rapid digitalization. The normal rhythm was occasionally interrupted by showers of extrasystoles, although the digitalis was reduced to a maintenance dose of 1½ gr. daily beginning March 15. Accentuation of the second pulmonic sound became marked, and reduplication of the first sound appeared over both the aortic and pulmonic areas. This gave way to a systolic murmur over the mitral, aortic and pulmonary valves. On March 20, a tender pulsating mass appeared in the right lower quadrant of the abdomen. Durozíez's sign was prominent over this pulsating tumor, which disappeared 2 days later. The left border of cardiac dullness on percussion was found to be in the 6th interspace, 13.5 cm. from the mid-line. The cardiac sounds finally became loud and booming and could be heard readily throughout the entire chest and abdomen, both anteriorly and posteriorly. The head and neck were seen to jerk and throb with each systole. On March 29, the day before death, a large, tender, pulsating mass appeared in the left upper quadrant, rapidly filled this area, and ballooned outward to the level of the umbilicus. A loud bruit was present over this tumor, which was thought to be a portion or a knob of the aneurysm, since no splenic notch could be felt and the blood picture remained essentially normal.

Probably the most interesting finding on physical examination was the discrepancy in the blood pressures in the two lower extremities. On March 15, a second electrocardiogram revealed inversion of T_2, with T_4 diphasic. On this same day it was noted that the pulsation of the dorsalis-pedis artery was more pronounced in the left foot than in the right. Unfortunately, comparative blood-pressure determinations in the legs were not made until 3 days later, when the reading in the left leg was 248/106 and in the right leg 156/104. This discrepancy was still present on March 22, when readings of 244/105 and 140/98 were obtained in the left and right legs respectively. On March 25, identical readings (182/90) were found in each extremity.

Two days later, the patient's general condition seemed quite encouraging, and it was hoped that his improvement might continue. Since the pulsating mass in the right lower quadrant was no longer present and since the blood pressure readings had become equalized of their own accord, it was hoped that the periaortic aneurysm had dissected back into the main aortic channel just above the level of the iliac bifurcation, forming the so-called "double-barrelled aorta." If this surmise had been correct, it was thought that a fatal outcome might be postponed for a considerable length of time.

On March 28 and 29, however, diarrhea and gaseous distention became increasingly distressing. A large, tender, pulsating mass appeared in the left upper quadrant, rapidly filling the epigastrium and extending down to the level of the umbilicus. There was no change in the blood pressure or in the blood picture, but the temperature rose to 101°F. It was believed that this condition was due to further dissection of the aneurysm below the diaphragm; the prognosis therefore became very uncertain.

Early on the morning of March 30, the patient experienced mild precordial pain, which was relieved by aminophylline. At 8:00 a.m., he stated that he felt fine and had no pain. Forty minutes later, he suddenly went into shock, and died while lying quietly in bed. The respirations persisted spasmodically for at least 3 minutes after the heart ceased beating. The picture during the agonal stage was one of exsanguination.

The final clinical diagnosis was dissecting aneurysm of the aorta, with death due to rupture of the aneurysm and massive internal hemorrhage.

Autopsy. Post-mortem examination, performed 8 hours after death by Drs. R. E. Miller and W. M. Downing, of Hanover, New Hampshire, showed an extensive retroperitoneal hemorrhage to the left of the mid-line from the splenic flexure of the colon down to the perirenal region and into the left portion of the pelvis. The peritoneum in these areas was dark red and purple owing to the underlying blood, but there was no evidence of intraperitoneal hemorrhage.

The right pleural cavity was dry, smooth and glistening. In the left pleural cavity, approximately 3 liters of hemorrhagic material, with massive blood clots in the dependent portion, was present. At the junction of the arch of the aorta with its ascending portion, an orifice 0.5 cm. in diameter was encountered, which communicated with the left pleural cavity. This was the point of rupture of the dissecting aneurysm. The pericardium was not involved, and the heart itself appeared essentially normal with the exception of sclerosis of the aortic valve (Grade II), and extensive sclerosis of the root of the aorta and of the coronary arteries (Grade III). The peri-intimal tissue in the lumbar regions and the perirenal fat on the left side were found to be heavily infiltrated with hemorrhagic material. At the point where the left subclavian artery arose from the arch of the aorta, there was a break in the intima of the aorta forming an orifice 0.3 cm. in diameter that communicated with a space in the peri-intimal adventitia extending from the region of the left subclavian artery down to the point of bifurcation of the common iliac vessels (Fig. 2). This peri-intimal space did not completely surround the aorta at any point, but was filled with clotted blood. Five centimeters distal to the intimal rupture marking the origin of the dissecting aneurysm was located the point of rupture of the aneurysmal sac into the left pleural cavity. The peri-intimal clot surrounding the right common iliac artery was so large that the true lumen of the vessel was markedly narrowed.

FIGURE 2. *Photograph of Post-Mortem Specimen.*

This shows the aorta lying within the aneurysmal sac, which has been opened longitudinally and is seen to extend from the arch of the aorta to the bifurcation of the iliac vessels. The portion of the ruler marks the point of perforation of the dissecting aneurysm into the left pleural cavity.

Microscopic study of the aorta revealed the usual histologic changes associated with arteriosclerosis. There was no cystic necrosis of the media, and no evidence of syphilis. The secondary aortic lumen caused by the dissection of the aneurysm was lined in part by endothelium, overlying organized thrombus.

Examination of the remaining viscera revealed no contributory findings.

Anatomic Diagnoses: Arteriosclerosis of the aorta, dissecting aneurysm of the aorta, with rupture, and hemothorax, left.

SUMMARY AND CONCLUSIONS

A case of dissecting aneurysm of the aorta diagnosed on the first day of the disease is reported. The cause of this aneurysm was undoubtedly arteriosclerosis. At the time of the attack, there was no sudden or violent physical exertion, since the patient was sitting quietly at his desk. The period of comparative well-being following recovery from the initial shock in this case is quite typical of dissecting aneurysm. Unfortunately, the patient followed the majority of victims of this disease in having his career terminated by sudden death on the nineteenth day.

The differential diagnosis between coronary thrombosis and dissecting aneurysm of the aorta is stressed.

Dissecting aneurysm of the aorta is a common cause of sudden death. The prognosis is poor, and approximately 80 per cent of the patients die within the first day or two. Treatment consists of rest, sedatives and appropriate supporting measures.

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MEDICAL PROGRESS

CONTROLLING CLINICAL THERAPEUTIC EXPERIMENTS WITH SPECIFIC SERUMS*

With Particular Reference to Antipneumococcus Serums

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BOSTON

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THE title of this paper might lead the reader to expect a scholarly dissertation including a historical review of attempts to control therapeutic experiments with biologic agents in human beings. Actually, it is the main purpose of this review to recount in an informal but critical manner some ten years of personal experience with attempts to determine the actual value of antipneumococcus serums in the treatment of pneumonia. Earlier data bearing directly on this problem were not very extensive and were quite inconclusive. Even when one turned away from pneumonia to other infectious diseases in which serums had been used, one could gain little either from the evaluation of the methods used or from the results obtained. At that time, there were at least three important diseases for which specific serums were available and had been used on a large scale with some attempt to control the results.

DIPHTHERIA

Perhaps the most successful therapeutic serum, and the one that has become definitely established as effective, is diphtheria antitoxin. This agent was introduced in 1890 by Behring, and was first widely used in human beings following the preparation of antitoxin in horses by Roux and Martin in 1894. It has been used in England and in the United States since 1895, and one of the first places where it was introduced successfully in this country was at the South Department of the Boston City Hospital. There is little question of the efficacy of antitoxin in neutralizing the lethal toxin of the diphtheria bacillus in animals. Efficient methods of preparing and titrating this antitoxin soon became available, and refinements of these methods were made as time went on. When one reviews the available data in an attempt to determine whether the use of this agent is actually effective in reducing the mortality from diphtheria, one is confronted with "a great body of evidence that can be adduced in favor of the treatment . . . much of which can be interpreted in other ways."[1] For example, from previous experience, there is reason to believe that the severity of the disease is cyclic. Much has been acquired in the form of education in the recognition and early treatment of the disease. Hospitalization is more frequent, with accompanying improvement in general care. There have been improvements in general hygiene and diet that have perhaps increased individual resistance to infections. Much has been learned concerning the care of the patient with laryngeal diphtheria in the way of intubation, and reduction in mortality from tracheotomies probably resulted. The relative significance of these factors in reducing the mortality from diphtheria is hard to evaluate.

In 1923, Andrewes,[1] in a review for the Medical Research Council in England, summarized the evidence up to that time in two categories, one of which he termed "evidence of first-rate value" and the other "evidence of secondary value." Some of the data in these categories are worth considering.

Unfortunately, only two therapeutic experiments could be classified as evidence of first-rate value. One was that of Fibiger,[2] in Copenhagen, the report of which was published in 1898. This worker treated all cases admitted to the diphtheria wards on one day with serum, and those admitted on alternate days were treated without serum. There were, of course, some cases in which the diagnosis was never definitely established. If these cases are excluded, there were 239 cases treated with antitoxin, with 8 deaths, or a 3.3 per cent mortality, as compared with 245 patients treated without antitoxin, among whom there were 30 deaths, or a mortality of 12.2 per cent. There can be little criticism of this type of alternation of cases, since it is extremely unlikely that on the "treated" days one would have a group of severe cases and on the "untreated" days a milder group, or that any other factors might enter into consideration that would detract from the value of the data presented. The total number of cases was rather small. I hesitate in this discussion to

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introduce statistical analyses, since this review is concerned with attempts to demonstrate unequivocal value in clinical experiments, and it has always seemed to me that when such value is not definitely apparent, the application of statistical analyses serves only to salve the conscience of the person who presents the data. This is particularly apt to be true when there are many variables and only a limited number of data. Nevertheless, Topley and Wilson,[3] in applying approved manipulations to these data have shown that the error of difference was 2.45 per cent, which makes the odds several thousand to one against the possibility that the data were a matter of chance.

The second experiment that Andrewes considered to be of first-rate value was that of Roux and his co-workers[4] in Paris in 1894. They treated with serum all the cases at the *Hôpital des Enfants Malades* from February to July, inclusive. They had a group of untreated controls, which were compiled from previous records of the same hospital, and in addition they observed the patients in the neighboring *Hôpital Trousseau* during the same period. When the experiment was over, they had 448 patients treated with antitoxin, of whom 109 died, a mortality of 24 per cent. In the untreated cases in the same hospital during the four preceding years, there was an annual mortality varying from 48 to 56 per cent, and an average mortality for the four years of 52 per cent. In *Hôpital Trousseau* from February to June, inclusive, there were 520 untreated cases with 316 deaths, or a mortality of 60 per cent. To overcome any objection that might be raised to the diagnosis, these authors further presented their cases of "croup" (laryngeal diphtherias) separately. They selected this group because the diagnosis of diphtheria in such cases can almost invariably be verified. To be sure, one frequently encounters cases of streptococcal laryngitis that are confusing at least during life. Nevertheless, before the introduction of antitoxin, the annual mortality in these cases of croup ranged from 68 to 75 per cent, and the average for the four years was 73 per cent. During 1894, the cases treated with antitoxin had a mortality of 49 per cent. Although this showed a definite reduction, it is certainly a smaller reduction than that for the entire group. There was further extracted from the total data a group of bacteriologically proved cases. Of these, 300 were treated with serum, with 78 deaths, or a 26 per cent mortality, as compared with a 50 per cent mortality in previous years when serum was not used.

The objections to these two experiments are that the numbers of cases were rather small. In each, the results were obtained during a one-year period only, and one cannot help wondering about two groups of cases in which the mortality in untreated cases in one community was 50 per cent and in the other about 12 per cent. There have been a number of attempts to repeat carefully controlled experiments with alternate cases, but these have always been abandoned because of the bad results in untreated cases.[5] All these attempts have revealed one outstanding feature in therapeutic experiments: as soon as most persons are convinced that the remedy is effective, it becomes impossible for any human therapeutic experiments to be carried out to a logical conclusion. Similar controlled experiments with Type 1 pneumonias have been tried at the Boston City Hospital. These were likewise rapidly abandoned when it was considered that many of the unfavorable results in the untreated cases could definitely have been averted by the use of serum.

In regard to evidence of secondary value, there are many facts that come from large masses of data concerning case mortality. In particular, this concerns the mortality rates before and after the introduction of antitoxin in the same general types of cases, such as those admitted to the same hospital or those occurring in the same community. The data also concern large-scale vital statistics from communities where infectious diseases are reported and the causes of death are tabulated. In a general way, large-scale mortality figures are not very reliable because they depend largely on the incidence of the disease as judged from reported cases in which the diagnosis is not always correct. Hospital figures are somewhat more reliable because the diagnosis is likelier to be consistent if the same observers have been interested in the condition, both before and after the introduction of the remedy in question. An example of such data is provided by the figures from the Metropolitan Asylums Board of London.[6] Before 1895, there was a steady mortality rate of approximately 30 per cent, which fell rather sharply after the introduction of antitoxin, to be stabilized after a few years at the mortality that has since been between 10 and 12 per cent. Similar figures from the Boston City Hospital, presented by McCollum and Place,[7] are of the same character.

In addition to these two types of data, abundant experiences from innumerable physicians more or less uniformly attest to the efficacy of serum. Although the individual experiences are far from convincing and are open to many criticisms, particularly since the data are usually not collected in a carefully controlled manner, the sum total

of this type of data is perhaps the most potent factor in establishing and maintaining this treatment as a "must."

Andrewes[1] summarized the evidence concerning diphtheria as follows, "There is sufficient first-rate evidence, backed up by a mass of statistics of secondary value and a great body of professional opinion, to show that antitoxin is of utmost value in human diphtheria." This was essentially the status of diphtheria antitoxin up to 1923.

Very soon after this publication, it became known that the disease apparently reasserts itself from time to time and produces high mortality rates even in spite of antitoxin therapy. Thus, in two large hospitals in Berlin, the mortality between 1923 and 1926 varied in one between 6 and 17.4 per cent, and in the other between 5.9 and 11.1 per cent.[8]

Another element of doubt is introduced into the absolute value of the previous data by a new factor, to which attention was called in 1933 by groups of workers in Leeds[9] and in Manchester.[10] These investigators, in a bacteriologic study of diphtheria cases and carriers, noticed three distinct types of diphtheria bacilli that could be identified on potassium tellurite blood agar and were defined further by means of sugar reactions. These were classified into the so-called "gravis, mitis and intermediate types," each of which has distinctive characteristics. It soon became clear that the severity of the disease in human beings corresponded to the types with which they were infected. Experimentally, it has been difficult to correlate these types with differences in the value of antitoxin produced in the immunization of animals, that is, in the protection which antitoxin against any one type affords against the toxin of these three different types. Nevertheless, in the experiences both in Leeds and in Manchester, the mortality in serum-treated cases was strikingly different, depending on the type of diphtheria bacillus cultured from the patients. In Leeds, there were 425 cases of gravis infection, with a mortality of 13.1 per cent; 24 intermediate infections, with 8.7 per cent deaths; and 113 mitis infections, without a single death. In Manchester, the results were similar, although the distribution of cases was somewhat different: 443 gravis cases, with 15 per cent deaths; 168 intermediates, with 7.7 per cent deaths; and 198 mitis cases, with 0.5 per cent deaths. The complications of the infections associated with these types likewise corresponded both in frequency and in severity to the mortality rates. Since then, it has been noted that the frequency of the types varies considerably in different communities and at different times. For example, the mitis cases have constituted from 8 to 92 per cent of the total in various groups of cases. This alone may account for wide differences in mortality rates.

Topley and Wilson,[3] in discussing the value of the data concerning diphtheria, conclude with these remarks:

> That it is still possible to bring forward contrary arguments that are not altogether specious is due to the fact that once a strong presumptive case has been made out in favor of a particular therapeutic measure it is not justifiable to continue the period of trial at the risk of human lives.

The recent results concerning the treatment of diphtheria and the reports of numerous outbreaks in Germany before the present war are certainly not acceptable as evidence for the efficacy of diphtheria antitoxin without the earlier control trials already mentioned. It is also to be borne in mind that, first, the downward trend in the general mortality from diphtheria preceded the introduction of antitoxin; secondly, the diagnosis of diphtheria has been made oftener in recent years, and milder cases are therefore included; the case fatality rate therefore goes down. This argument applies, perhaps, somewhat less to laryngeal diphtheria, in which the diagnosis was probably quite accurate before the introduction of antitoxin, and in this group, the mortality in cases without tracheotomies in a large collected series has dropped from 62 to 17 per cent since the introduction of diphtheria antitoxin, as evidenced by the figures from the South Department of the Boston City Hospital.[7]

Meningococcal Meningitis

The etiologic relation of the meningococcus to epidemic meningitis was demonstrated first in 1887, and antiserum against meningococcus was first prepared in a polyvalent form by Jochmann in 1906. He treated 17 cases by subcutaneous and intraspinal injection of this serum, and 12 of his patients recovered. Flexner,[11] in 1913, tried out various methods of preparing serums, and distributed to a large number of physicians and hospitals the serum that he considered most potent, and then collected results and analyzed them. It has always seemed to me that this is an unreliable and even misleading method of demonstrating the efficacy in actual human therapy of an agent that is effective in animal experiments. The arguments that can be adduced to detract from the value of a therapeutic experiment based on distribution of an agent to a large number of physicians in various communities or in hospitals — no matter how reliable the physicians themselves are — are too numerous to mention. In particular, it is impossible under such conditions to obtain

proper controls. In Flexner's accumulated data, there was a mortality of 31 per cent after the exclusion of all cases in which deaths occurred within twenty-four hours, all chronic cases and all patients who were moribund when first treated or in whom there were mixed or intercurrent infections. This figure was compared with the mortality in untreated cases, from which no exclusions were made and which varied from 42 to 80 per cent, averaging 70 per cent. In the treated cases, the efficacy of therapy was shown to vary with the time at which it was administered. It was most effective if given within the first three days of the disease. Cases treated during this time had a mortality of 18 per cent, those treated from the fourth to the seventh day had a mortality of 27 per cent, and those treated after the seventh day, 37 per cent. Flexner also showed a relation to age, with the highest mortality in the group under one year of age and the lowest mortality in the group between five and ten years. Clinically, the most rapid recovery occurred in the favorable age group, and there were fewer complications among the treated cases.

Dopter[12] summarized the French cases treated with serum from the Pasteur Institute. In his series, there was a mortality of 14.5 per cent before exclusion of the moribund cases and those complicated with other infections, and 11.7 per cent after such cases were excluded. In cases treated without serum, the mortality during the same period was 65 per cent.

Experiences with antimeningococcus serums first brought out the importance of type specificity. Specific types of meningococcus were recognized and classified in 1909 more or less simultaneously by three different workers. Hine,[13] in reviewing the results of serotherapy in some of the British forces during World War I, showed that the treatment was highly effective in Type 1 and Type 3 cases, and was much less satisfactory in Type 2 cases, but the number of cases was small. In his first series, there were 90 cases, 34 of which were Type 1, with 1 fatality; 10 were Type 3, and all these patients survived; and there were 7 deaths among 32 Type 2 cases. He emphasized the value of early treatment, daily doses, prompt typing, adequate use of the appropriate serum and the administration of large doses for Type 2 cases. These arguments have become commonplace, since the various therapeutic experiments with antipneumococcus serums emphasized the significance of each of these points. In a second series, including moribund patients but excluding those with intercurrent diseases, there were 141 cases, with 19 per cent deaths among those treated within the first six days. There were 65 cases with 9 per cent deaths among patients with Type 1 infections, 39 per cent among 104 with Type 2, and 25 per cent among 28 with Type 3. Unfortunately, an epidemic of influenza intervened at the time of the second series, so that part of the mortality may have been due to that cause. There were 48 untyped cases in this series, with a mortality of 45 per cent.

Numerous reports concerning the use of antimeningococcus serum have appeared since the early studies of Flexner and Dopter. Not all have been quite so favorable. One carefully controlled study carried out in Detroit by Gordon[14] shows how any one group of figures collected over a limited period might be misleading. In his report before the Association for Research in Nervous and Mental Diseases in 1931, Gordon tabulated the mortality from meningococcal meningitis in the Detroit area and from the Herman Kiefer Hospital for the years 1922 to 1931. All the cases during this period were treated with serum. The mortality in the endemic years 1922 and 1923 was 65 and 55 per cent, respectively. In the pre-epidemic years 1924, 1925 and 1926, the mortality was 19, 14 and 41 per cent, respectively. In 1927, there began an epidemic that reached its peak in 1929 and subsided in 1931. During this period, the mortality rose sharply to a peak of 65 per cent, and then dropped to 42 per cent. For the most part, only one type (Type 3) was found to be the causative agent. The serum at first was polyvalent with a low titer for Type 3, but was later monovalent and of high titer. The results indicate clearly either that the efficacy of antimeningococcus serum was misjudged or that other factors were introduced which militated against the best results. One point might be mentioned that has been illustrated in the low figures of 19 and 14 per cent, which Gordon reported for the endemic years 1924 and 1925, namely, in some endemic periods the mortality may be low, or during such periods good serums may be available against the particular strain that causes the infection. This feature is also brought out in the striking results that Tillett and Brown[15] reported from Johns Hopkins Hospital during the spring of 1935, when they had only 1 death among 25 consecutive treated cases.

Tillett and Brown's results, although not conclusive, may hold the answer to another secret concerning mortality, which has been perhaps more clearly revealed in the use of antipneumococcus serums. They employed serums prepared in the New York State Laboratory. These serums were of uniform quality and of high potency against the particular type with which they were

concerned. Although their cases were not typed, the strains subjected to serologic classification all fell either into Group 1 or into what they called Group 1–3. The serums included both concentrated and unconcentrated lots, but all of them contained high titers of antibodies (by the various laboratory criteria used) against the particular type that occurred in this series. They also used larger doses of serum, and this may have been an important factor in the low mortality.

In determining the value of antimeningococcus serum, one is thus left with a peculiar impression similar to that following the early use of antipneumococcus serums, namely, that one is dealing with an agent that is apparently effective, but conclusive proof of its effectiveness is lacking. Most of those who used the serums noted the rapid clinical improvement in the patients who responded; the best results occurred in the cases treated early and in the young patients, except infants. Nevertheless, considerable conflicting data concerning mortality in different communities, and at different times in the same community, leave an element of doubt concerning what relation the drop in mortality ascribed to the use of serum actually has had to the variations in the disease at a particular time and place. The use of antimeningococcus serums is already involved by many of the same problems that later confronted workers concerned with the treatment of pneumonia: type variations, differences in mortality among the types and in different age groups, variations in the potency of serums and difficulty in estimating such potency by laboratory tests, the results of which have any correlation with clinical efficiency.

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Anterior Poliomyelitis

The problem of evaluating the use of convalescent serum in the treatment of anterior poliomyelitis presents an even more complex situation. In the first place, there is involved a serum that experimentally has been shown to have only what have been called "neutralizing antibodies."[16] There is no evidence that convalescent serums or antiserums prepared against the virus in experimental animals are of any value in curing disease or in preventing paralysis even in animals, once the infection has taken hold. It is obvious that human beings cannot be treated at the same time that the virus is introduced. Therefore, theoretically, convalescent serum has no standing as a therapeutic agent, even on an experimental basis. Nevertheless, it has been accepted widely. It was only after attempts had been made to reinvestigate the problem by carefully controlling the results that any element of doubt concerning the value of the serum was introduced.

In this disease, the mortality has shown wide variations in different epidemics, and even within the same epidemic in different communities. Similar variations in extent and severity of the paralysis have occurred during the same epidemic. Comparisons between cases that were serum treated and those that were not have been most difficult. One is dealing with a therapeutic agent accepted more or less on faith and used because in this disease no other effective therapy is available. The results, as reported, have been accepted without criticism. In 1932, Kramer and his associates[17] presented the results of their experiments in Brooklyn, and Park,[18] at the Association of American Physicians, presented the results of a large experiment undertaken jointly by the New York City Department of Health and the New York Academy of Medicine. These studies indicated that in two large contemporary series of cases the mortality and the extent of paralysis were almost identical, and, in fact, that the differences observed were slightly unfavorable for the serum-treated cases. The results were disbelieved by some workers and merely ignored by others,* but they have since been confirmed.[19]

Pneumococcal Pneumonia

Before turning to the immediate problem concerning pneumonia, one should consider some of the factors that are involved in determining the therapeutic efficacy of an antiserum for human patients after its beneficial effects in experimental animals have been clearly demonstrated. The chief factors may be listed as follows: the problem of diagnosis, including both the clinical and the etiologic diagnosis; the factors in the parasite or the invader; the factors in the host; the factors concerning the antiserum; the extent to which the host and the invader have interacted at the time when the antibody is administered; and the complications of the infection.

In diphtheria, the diagnostic problems are not very difficult. Treatment usually can be administered on the basis of clinical diagnosis, and the etiologic diagnosis is not too difficult to establish or to verify. The host is usually a young person, and complicating conditions in the host are not important factors. In infants, the prognosis is poor, as in most other severe infections, and

*Here again, one observes the mixed motives that sometimes confront the laboratory scientist when he is concerned with clinical experimentation. In discussing Park's paper, Flexner[18] stated: "There is a consensus . . . that the use of convalescent serum does no harm. Since it cannot be affirmed that in an individual case it does no good, should its use be withheld? This is a question to be answered not by a pathologist but by a practitioner." Many a budding clinician hoping to bring a strict "scientific attitude" to bear on some of his bedside problems felt a bit disarmed by these remarks.

specific serum therapy is least effective. The infecting organism in diphtheria was formerly thought to be uniform in its virulence and toxin production, but it is now recognized that both these factors may vary, as already noted. This factor is the most significant in considering the value of previous reports on this disease. Standardization of the antibody has been fairly well established. Antitoxin is comparatively uniform in quality, at least within the range necessary for therapy. Even on this point, however, there is now some doubt, since the relation between the antibodies produced by toxin from the various types of diphtheria bacilli cannot be evaluated properly at the moment. It is recognized in diphtheria, as in other diseases, that the earlier the treatment is undertaken the better the results. This is corroborated by fairly reliable data. Most reports that deal with numbers large enough to be of value, however, indicate that antitoxin has a definite effect at any stage of the disease. The reason why the results of the therapy of diphtheria in certain recent epidemics have been less favorable than in the past is now ascribed to the occurrence of the gravis organisms. The effectiveness of antitoxin against infections with this type will have to be re-evaluated. Complications of the infection itself are related directly to the action of the toxin, or to mechanical complications in laryngeal involvement. The incidence of laryngeal diphtheria and the methods by which this form of the disease is handled, aside from the specific antitoxin, are also major factors in the fatality rates in the serum-treated cases.

The diagnosis of meningitis is usually not difficult, especially in epidemics. The host factors are not much more disturbing in this disease than in diphtheria. The problems concerning the invader are important, since the mortality from different types varies considerably, and since the efficacy of the serums against each type is apparently also quite variable, being most effective against the Type 1 and least effective against the Type 2. The antibody presents difficulties in standardization that have not yet been entirely overcome. The use of in vitro tests, such as the agglutination, complement-fixation and precipitin tests, has not always paralleled the results of protection tests, which are difficult to standardize. The stage of the disease when treatment is begun presents the same problem as that of diphtheria. The complicating factors in the treatment of meningitis are such as may interfere with the efficiency of treatment; for example, the development of spinal-fluid block or the deposit of thick layers of fibrin that enclose collections of purulent material not amenable to drainage. These complications may maintain the organisms locally after the general infection has been overcome.

In poliomyelitis, the diagnostic problems are difficult to evaluate, particularly since they have been complicated with the question of so-called "preparalytic poliomyelitis." The etiologic diagnoses are made essentially on clinical grounds and cannot at present be established. The hosts are usually young. The problem of variations in virulence of the invader is recognized but not understood. The serums are practically impossible to standardize at the present time, so that the entire choice of specific therapy in poliomyelitis rests on rather precarious grounds, as demonstrated in the most recent therapeutic experiments.

At the time when the attempts to evaluate serum therapy in pneumonia were first made in a serious manner at the Boston City Hospital,[20] there were difficulties on all scores. Some of these problems have since been solved, but most of them still remain. Since treatment was then limited to cases of typical lobar pneumonia, the clinical diagnosis was relatively simple. Etiologic diagnosis was complicated by the fact that treatment required type-specific antibody, at least so far as could be ascertained from animal experiments. Type diagnosis was then still a time-consuming matter. There was, in addition, the difficulty of determining the etiologic relation to the disease of any pneumococcus type found in the sputum, since that was the main source of material for typing. The occurrence of bacteremia in any given case usually solved the problem of the etiology for the particular patient concerned. Even this fact, however, frequently became known only some time after a type diagnosis had been made from the sputum. There was also the factor of mixed infections, since it is rare to obtain pure cultures of pneumococci from sputum, particularly in the early stages of the disease when serum might be expected to be most effective. Host factors in pneumonia were obviously of the greatest consequence, particularly in large municipal hospitals, where a great number of the patients are in old age groups and suffer from degenerative diseases. Many of the patients of all ages may be affected to some degree by nutritional disturbances, and a great many adults suffer from chronic alcoholism. With respect to the parasite, there was of course the problem of specific types of pneumococci already mentioned. In addition, the possibility that the virulence might vary from year to year, even with the same type, was a factor. The extent to which the host and the invader have interacted at the time that specific treatment is begun is, of course, most significant

in cases of pneumonia. This became clear from the very start when the attempt was made to treat patients regardless of how long they had been sick.[20]

The antibody itself presented more than its share of difficulties. Part of the problem later on concerned the evaluation of the toxicity of various lots of serum. It was soon recognized that serum reactions were entirely independent of antibody content and interfered considerably with the therapeutic end results. In fact, these untoward reactions often made it impossible to use some lots of serum. The methods of refining and concentrating antibody were being developed at the same time, and considerable controversy was aroused among some workers about the relative antibody content and therapeutic value of concentrated and unconcentrated serums. The controversy hinged on the procedures used in evaluating potency, which until recently depended solely on the mouse-protection test.

Complications from pneumonia may, of course, in themselves be fatal, even after the acute disease in the lung has subsided. They are recognized as occurring in the severest cases and in those in which invasion of the blood stream has occurred, but they usually appear late in the disease. Thus, the question of delayed therapy is intimately related to that of complications.

All the early studies were carried out with horse serums. Antibodies of high titer were attained in horses with great regularity against Type 1 pneumococci, but Type 2 antibodies were difficult to produce in high titer, and different horses varied considerably in this respect. The Type 3 pneumococcus presented a hopeless problem, since significant amounts of antibody for this type could not be produced. After the newer classification of pneumococci became established, it was recognized that some of the new types, which were most prevalent, were highly antigenic in horses, and good titers against them were regularly obtained. Notable among these was Type 5. More recently, it has become possible to produce in rabbits highly potent therapeutic serums against all types of pneumococci.

At the Boston City Hospital, there had been two clinical experiments in the serum therapy of pneumonia before Sutliff and I began our studies. The first was that of Locke and the workers on the Pneumonia Service, which was organized during the great influenza epidemic and continued through the year 1922. Locke[20] attempted to carry out a very carefully controlled study with the Type 1 serum prepared in the Massachusetts Antitoxin and Vaccine Laboratory according to the methods developed at the Rockefeller Institute. The results at the Rockefeller Institute, as well as those in other clinics, were not very convincing. There were no controls. Locke, during the first year of his study, treated all Type 1 cases, and during the subsequent two years treated a strictly alternated series of Type 1 cases. The final result in groups of about 70 cases each showed an almost identical mortality in the first year, when all Type 1 cases were treated, and in the second year, both in the treated cases and in the alternate control cases. The only indication that there might be some curative value in the serum that he employed appeared from the results of the 12 treated cases in which the serum was given before the end of the third day of illness. None of these patients died. Locke was dealing with unconcentrated serums, whose potency may have been extremely low, as later shown by Felton and Stahl[21] in their survey of the problems of standardization.

It is interesting that the mortality from Type 1 pneumonia in each of Locke's three series was about 17 per cent. A more careful survey of these cases shows that during the first period there was but a 17 per cent incidence of bacteremia, and that during the second period, the treated cases had a bacteremic incidence of 44 per cent, as compared with 22 per cent among the controls. All the studies in both treated and untreated cases during the last ten years have indicated that the mortality is directly proportional to the bacteremic incidence. In untreated cases, except in those due to Type 3 pneumococcus, which are almost invariably fatal if the blood is invaded, the bacteremic incidence practically tells the mortality in any group of cases.[22]

Following Locke's study and beginning in the year 1924, the Department of Preventive Medicine and Hygiene of the Harvard Medical School became interested in a therapeutic experiment at the Boston City Hospital. In this study, alternate cases were treated with various lots of serum, which Felton had prepared by various methods of concentration. The study was conducted by a single resident, who was under the general direction of Felton, and had the clinical supervision of Locke and Robey. This resident obtained sputum for typing and treated alternate cases that were called to his attention in which a definite clinical diagnosis of pneumonia was made. The records of both treated and control cases were turned in to Felton. There was a different resident each year, and when I undertook the studies there had been five years of this experiment. From

the records available for these years, an attempt was made to analyze the results of the serum therapy. Utilizing the experience of Locke and also considering that the experiment was done with bivalent serum containing Type 1 and Type 2 antibody, we attempted to learn: whether the serum therapy produced a reduction in mortality; whether the reduction was greater in the cases due to Types 1 and 2 pneumococci than in the others; and whether the patients treated early in the disease were benefited more than those treated late. It was also of interest to learn whether this rather impersonal method of handling a therapeutic experiment resulted in reliable and comparable groups of treated and controlled cases.

The mortality figures[23] showed that the cases of Type 1 and Type 2 pneumonia treated within the first three days of the disease had a definitely lower mortality than the untreated cases, or than the cases treated on the fourth day or later. The disturbing feature was an apparent reduction in total mortality in the Type 3 and so-called "Group 4" cases. These patients had received the bivalent (Types 1 and 2) serums, which contained no specific antibody for the types with which they were presumably infected.

It was assumed that the successive residents treated alternate cases as long as they had serum, discontinued their experiments when no serum was available, and kept records only during the time that the experiment was going on. It was of some interest, therefore, to find out to what extent two important factors might have influenced the choice of cases: one was the stage of the disease, and the other was the age. In other words, it was essential to determine whether a larger proportion of the younger patients and more of the patients admitted early in the disease might have been treated with serum to account for the differences in mortality in the serum-treated Types 3 and 4 cases. It has been well recognized that mortality in pneumonia, regardless of the etiologic agent, increases with advancing age. If a larger number of old people were included in any groups, obviously the gross mortality figures would be influenced unfavorably. On analyzing the data on this point, it was easily shown that the so-called "control cases" had a definitely unfavorable age distribution. This was also true of the distribution according to the stage of the disease. Among the serum-treated cases, a larger percentage were admitted early in the disease, and fewer late cases were included. To offset this factor and at the same time to obtain some idea of the effect of serum on the course of the disease, it was necessary to compare the total duration of the acute disease in the Type 1 and Type 2 treated cases with that of similar patients who were not treated with serum and who were admitted to the hospital at the same stage of the disease. This was done by comparing the average total duration of the acute disease (using arbitrary but similar criteria) with the duration of the illness at the time of admission to the hospital. In this way, it was shown that the duration of acute illness was shortened in Types 1 and 2 cases by early serum treatment. Also, among the Type 1 cases, composite temperature charts were constructed for the patients who recovered without complications, one for those treated with serum, and another for those who were not treated with serum. When these composite temperature charts were constructed so that they began with the first day in the hospital, differences between the treated and the untreated groups were not apparent. However, a rearrangement of the data according to the day of onset of the disease showed a definite reduction in the total period of febrile illness among the Type 1 treated patients who recovered.[23]

When, in 1929, Sutliff and I attempted to formulate further plans for the evaluation of serum therapy, it became obvious that it would not be possible, within a period short of several years, to produce reliable and significant evidence on the basis of mortality figures. We therefore attempted to use the results in individual cases as a basis for comparison, following treated and untreated cases very carefully and alternating serum therapy by a strict method, which was controlled entirely in the laboratory. Serum was given to alternate cases of each type as soon as the type was determined. From the very start it became obvious that such controls were only self-deluding. We were confronted with patients in whom the type was determined after the patient was already dead, and others who were moribund when the results of the typing became known. We soon limited our experiments to those patients who, at the time the type was determined, were ill for four days or less. This, in addition to the fact that an ample supply of highly potent Type 2 antibody was available, made it possible to include both Type 1 and Type 2 cases in such an experiment.

The results from the point of view of mortality are difficult to evaluate because the numbers were small. The clinical effects of serum were determined by using the temperature and general symptoms as criteria. The results in Type 1 cases during the first year were thus tabulated. By all recognized criteria for clinical recovery, the termination of the disease in serum-treated cases was shown to be in relation to the time when the

type was determined, and thus to the time when the serum treatment was given. This was demonstrated clearly in this first year's experience, in which all Type 1 cases were included, regardless of the time of admission.[24] Similar results were demonstrated even more clearly in the cases of Type 1 pneumonia, both treated and untreated, during the next three years.[25] The duration of acute symptoms was always relatively short in treated cases, and comparatively long in untreated cases. Symptoms of the acute disease rarely persisted beyond the fourth day in the patients admitted early and treated with serum, and rarely ended before the fourth day in those who were not treated with specific serum. Similar results were also demonstrated in Type 2 cases.[26]

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During the time when only Type 1 and Type 2 serums were available, we tried to obtain as many data as possible on all other cases of pneumonia, from both the clinical and etiologic points of view. We attempted to type all cases in which pneumonia was suspected, followed them, and eventually analyzed the results with the hope of having a background for comparison when new serums or other remedies became available. A survey of these cases, as well as of those that were treated, showed certain constant features with regard to mortality: bacteremic patients always had a much higher mortality than corresponding patients without bacteremia; the mortality increased with advancing age; in serum-treated cases, there was a general correlation between the time of treatment and mortality, — the earlier in the disease treatment was begun the lower was the death rate; the greater the extent of the pulmonary lesion at the time when the patient was admitted to the hospital or when treatment was begun, the higher was the mortality; the development of infected focal complications increased the death rate; the occurrence of underlying acute or chronic disease had a marked influence in increasing the death rate in both treated and untreated cases.

As time went on and better serums became available for Type 1 and Type 2 cases, as well as for other types, it became clear that we were concerned as much with the problem of the conditions under which these serums were useful in reducing mortality or in cutting short the disease as we were in the general reduction in death rate.

During the early experiments with the serum treatment of pneumonia, as already mentioned, alternate patients were given the bivalent serum before the type determination was made. At that time, one feature of the effects of serum treatment was more impressive than any other. When a patient who had been ill for four days or less was admitted to the hospital and given serum, if he was well the next morning, the type was almost always found later to be either Type 1 or Type 2. This seemed to us at the time to be the best clinical evidence for the effectiveness and specificity of the serum, in spite of the fact that this was difficult to express in a convincing form, except by comparing the clinical course of the disease in treated and untreated cases in the manner already mentioned. However, when a larger body of data became available, which was sufficient to be analyzed into the factors that I have already outlined, the mortality figures also appeared to be significant and convincing. The available figures are illustrated in the reports[27] on the results of treatment in Types 1, 2, 5 and 7 cases during the nine-year period from 1929 to 1938.

The outstanding features of these mortality figures are: an increasing proportion of cases were submitted to serum therapy; a constantly low mortality was observed in those treated with serum; and a constantly high mortality was noted in patients who escaped serum therapy for one reason or another — many of the patients who escaped serum therapy in the latter years were diagnosed either after recovery or at autopsy.

In addition to the gross fatality rates, a large amount of clinical evidence based on the following facts has been gathered: there is a definite relation between treatment and recovery; bacteremia is arrested following serum therapy; the spread of the disease in the lung is arrested following serum administration; except in those treated very late in the disease, the mortality in serum-treated cases is always lower than in comparable cases not treated with serum — this is true in all age groups, in bacteremic and nonbacteremic cases, in those with limited or extensive lung involvement, and in those with and without complications or other predisposing conditions; and the beneficial results of serum therapy are strictly type specific.

Another important feature in the evaluation of the therapy has been the fact that in all but a very few cases, failures to obtain striking beneficial results following serum administration could be traced to certain well-defined causes. These are, briefly: delayed treatment; inadequate therapy or improper treatment in the sense of spreading dosage over a long period —the use of serums of low potency falls in this category; misdiagnosis, that is, etiologic misdiagnosis, which includes errors in typing and the improper evaluation of the relation of the bacteriologic finding to the etiology of the disease; the presence of focal

complications, notably empyema, at the time treatment is begun; and the pre-existence of severe systemic disease such as cardiac or renal failure, cerebrovascular accidents and alcoholic delirium. How or why these factors interfere with the results of therapy is not within the scope of this presentation. It is obvious that many of these conditions, which are unfavorable from the point of view of specific serum therapy, may nevertheless be influenced favorably by other types of treatment, as we have seen since the introduction of chemotherapy.

If an attempt is made to summarize our experience in pneumonia in relation to the experiences of others with various infectious diseases, we find that the actual attempts to demonstrate reductions in mortality by carefully controlled clinical experiments were not entirely successful and were essentially abandoned in favor of the careful observation of individual cases for the beneficial effects of serum or for the causes of the failure to obtain such beneficial effects. We were led to the belief that therapeutic antipneumococcus serum, if it were effective, should demonstrate its benefits in every case in which it is used unless definite and recognizable factors are present that militate against its efficacy.

In conclusion, it is probably safe to say that in the evaluation of treatment in a disease like pneumonia one must rely on the integrity of the reporter to present all the relevant facts. Only when all the details are presented is it possible to demonstrate the efficiency of the agent in question. The differences between treated and untreated cases must be unequivocal and must be consistent. Only in this manner can the reporter himself be really convinced of the significance of his results. The reader of his reports can become satisfied only when he goes through similar experiences and is likewise impressed with successive individual results.

The relation of serum therapy to chemotherapy is not strictly within the scope of this paper. However, since this is now the only problem of importance with respect to the use of serum in pneumonia, it will be considered briefly.

It is generally conceded that chemotherapy with one of the sulfonamide drugs, notably sulfapyridine or sulfathiazole, is now the treatment of choice in cases of pneumonia.* The question arises whether the use of specific serum in addition to one of these effective sulfonamides is more beneficial than the treatment with that drug alone. From what has already been said concerning the evaluation of antipneumococcus serums, it is obvious that this question is considerably more difficult to answer decisively on the basis of strictly controlled clinical studies.

Since adequate data have been brought forth to attest the efficacy of the sulfonamides, it is no longer possible to deny any patient with pneumonia the benefits of their use. Even a delay in the application of chemotherapy is justly open to criticism because with these drugs, as with other remedies, early treatment is essential for the best results. Furthermore, the ease of administering the drugs and the frequency and rapidity with which the pneumonias respond to their use make additional therapy useful, at best, only in selected cases that do not yield readily to the drugs alone. It is difficult to see how a clinical experiment that takes these factors into account can yield a decisive answer to the question at hand.

In the cases treated at the Boston City Hospital,[29] an attempt was made to compare the results of treatment with serum and sulfapyridine used separately and in combination, to determine the conditions under which each type of therapy might be most advantageous. The combined therapy was used in the severest cases, and in patients who did not seem to improve under treatment with one or the other agent when used separately. A large proportion of the cases in which the combination of serum and drug was used may, therefore, be classed as failures, or threatened failures, from chemotherapy. Similar data have been reported from most of the other clinics in which such studies have been undertaken. Obviously, no conclusions can be drawn from such data concerning the relative merits of the drug alone and of the combined therapy. Our results suggest that in most of the cases with the worst prognosis, the use of serum in addition to sulfapyridine may increase the chances of recovery and may shorten the duration of the acute illness in patients who survive. The results in individual cases, although they generally support this view, still leave room for doubts.[30]

In two recent reports, the attempt has been made to cope with this problem by setting up strict criteria for the choice and alternation of cases. Dowling, Abernethy and Hartman[31] alternated their cases within each type of pneumococcus as soon as the type was determined, one case being given sulfapyridine alone and the next receiving both this drug and serum. To avoid too great a delay in initiating therapy, every patient in whom the pneumococcal type was not obtained within six hours was excluded from the study and given sulfapyridine. In the patients who received the combined therapy, recovery was more rapid than in

*The relevant literature on this subject has recently been summarized.[28]

those treated with the drug alone, as judged by the average duration of fever. In the patients over forty years of age, the mortality was also lower with the combined treatment. The only serious objection to this study is the small number of cases involved.

In the second report, by Plummer and his associates,[32]* all patients were treated with some sulfonamide drug as soon as the clinical diagnosis was made, and alternate cases within each type were placed in the series treated by serum in addition to the drug. Some of the patients were already dead and others were afebrile at the time the type was determined; they received no serum, but were nevertheless retained in the group receiving combined treatment. From a comparison of the death rates and of composite temperature curves, these authors concluded that there was no significant difference in the results of treatment in the two series.

It is rather odd, in view of the strict alternation in type stressed by these authors, that for many of the types there is a preponderance of cases either in the series treated with the drug alone or in the combined-therapy series. The length of the delay before serum treatment was given in most cases is not mentioned, but in some of the cases it was as long as twenty-four hours. Furthermore, although mention is made of the number of patients who received serum and died within twenty-four hours, the total number of patients who actually received serum is not given. Moreover, a considerable portion of the mortality among the patients who received combined treatment occurred within twenty-four hours of admission to the hospital, whereas only a small number of those receiving the drug alone died within twenty-four hours of entry. Although it is possible to deduce from these data that some of the fatalities were the result of the serum therapy, it seems much more probable that some unconscious selection on the part of the authors played an important role in the inclusion of the poorest subjects among the serum recipients. This is only a natural occurrence, since there is always a tendency to give to the patients who seem the most severely ill the benefits of any remedy that is known to be effective. It is likewise natural, particularly in view of the time and effort required for serum administration, to avoid giving this type of therapy to patients who seem to be improving adequately without it.

The conclusions drawn by these authors may or may not prove to be correct, but one cannot help believing that the results as presented are not only inconclusive but even grossly misleading. It would likewise be erroneous to draw any conclusions regarding the relative merits of these two types of treatment from mortality figures obtained from reports in which the selection of cases was not strictly controlled. This is true of groups of cases from a single clinic, such as those I have presented,[29] but it is all the more true of cases gathered by central agencies from the reports of scattered physicians.

The two studies that have been discussed concerned adults. Another controlled study, carried out in infants and children, was reported by Carey.[33] He alternated his cases as soon as the diagnosis of pneumonia was made and the pneumococcus typing was completed. In cases in which the causative organism was found to be a pneumococcus for which specific antipneumococcus serum was available, alternate patients who were not serum sensitive received serum in addition to the drug. This alternation was not followed strictly because of certain patients in whom either typing was delayed or a mixed infection was present, and it was not immediately clear which was the causative type. In such cases, chemotherapy was started, and the patients were frequently well when the question of serum therapy arose. The fatality rates in all groups of cases were so low that comparisons were not justified.

The average duration of the disease was compared and was of some interest. It was found that the duration in the treated cases was the same after sulfapyridine as it was after sulfathiazole. The outstanding finding in this series, however, was that the average duration of the pneumonia after treatment was appreciably shorter in those patients who received specific antipneumococcus serum in addition to sulfapyridine or sulfathiazole, as compared with the duration of the acute illness after treatment with sulfapyridine or sulfathiazole alone.

The question whether the use of serum in addition to a sulfonamide is superior to the use of the drugs alone thus remains unanswered. It is my opinion that this particular question as it concerns pneumonia is now a highly academic one, since it is unlikely that any physician would contemplate using the combined therapy as a routine in all cases. It seems far more important to concentrate on the failures of chemotherapy and attempt to determine, first, whether such failures can be predicted, and then which of them can be averted by the use of serum. Even this is not a simple task. Fortunately for the patient with pneumonia, however, the failures from chemotherapy are few.

*A reply by Dr. Plummer to the criticism of his paper appears in this issue of the *Journal* (page 517).

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CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

ANTE-MORTEM AND POST-MORTEM RECORDS AS USED IN WEEKLY CLINICOPATHOLOGICAL EXERCISES

FOUNDED BY RICHARD C. CABOT

TRACY B. MALLORY, M.D., *Editor*

CASE 27391

PRESENTATION OF CASE

A thirty-seven-year-old man entered the hospital complaining of fatigue, hemoptysis and pain in the left arm.

Two years before admission, the patient noticed that he was becoming unduly fatigued, and that rest gave him no relief. He carried on until eight months before admission, when a small hemoptysis — about one teaspoonful — occurred, without other symptoms referable to the respiratory system. A chest plate was taken immediately, and a diagnosis of tuberculosis of the left apex made; the patient was sent to a sanatorium, where intensive studies were carried out, including x-ray films, fluoroscopy, lipiodol injection, bronchoscopy, a punch biopsy of the lung and sputum examinations. The patient was told that tuberculosis was definitely ruled out and that the most likely diagnosis was a low-grade infection of the lung, possibly due to a fungus. With sanatorium care and potassium iodide treatment, he improved and was able to return to work at the end of four months.

Eight weeks before admission, fatigue returned, and a dull gnawing ache developed in the left anterior chest. In addition, along the inner surface of the left arm immediately below the axilla, he noticed pain that gradually spread down the lateral surface of the arm as far as the mid-forearm. Both pains increased in severity, the arm pain becoming the more pronounced of the two. Six weeks before admission marked the onset of night sweats, which were still a symptom at the time of admission. Two weeks before entry, the patient went to Florida, but after several days developed a fever rising to 102°F. He entered a hospital, and the fever subsided within a few days; x-ray films were taken, and he was referred to this hospital. There had been a loss of 10 pounds in weight in the previous eight months. Cough and sputum were never very marked symptoms, the latter being limited to a half teaspoonful a day, raised in the morning and perhaps once again during the day. It consisted of brown purulent material.

On examination, the patient was well developed and well nourished and not in apparent distress. Examination of the heart was negative; the blood pressure was 130 systolic, 70 diastolic. In the upper left chest, from the supraclavicular fossa down to the third rib anteriorly and the fourth thoracic vertebra posteriorly, there was dullness to percussion, with diminished tactile fremitus and breath sounds, but no rales. The abdomen was normal except for a small right inguinal hernia.

The temperature was 99°F., the pulse 100, and the respirations 22.

Examination of the urine was negative. Examination of the blood showed a red-cell count of 4,330,000 with a hemoglobin of 13.6 gm. (photoelectric-cell technic), and a white-cell count of 8900 with 82 per cent polymorphonuclears. The nonprotein nitrogen of the blood serum was 28 mg. and the protein 6 to 7 gm. per 100 cc.; the blood Hinton reaction was negative. Repeated examinations of the sputum were negative for tubercle bacilli and actinomyces; cultures yielded rare colonies of beta hemolytic streptococci, with a predominance of alpha hemolytic streptococci.

An x-ray film of the chest showed an area of dullness occupying the upper portion of the left lung field. In films taken in the usual manner, the shadow appeared to be of homogeneous density and extended from the extreme apex to the third rib in front; the trachea and mediastinal contents were not displaced, and the diaphragm on this side was in the usual position and only slightly limited. The lung fields, except for the area described, were normal in appearance. The heart shadow was not increased in size or abnormal in shape, and there was no displacement. In a film taken with the Bucky diaphragm, the lower half of the shadow presented a mottled appearance, with dense lines running through it suggesting the walls of bronchi or trabeculation. The margins of the shadow were quite dense, and the lower border was convex. In the lateral view, the shadow appeared to extend from the anterior to the posterior wall, and its greatest extent was in the middle part of the chest. The trachea appeared to lie anterior to it; there was no visible pulsation.

A review of films taken in other hospitals showed that a little over two years before admission, the left apex was clear and there was no visible tumor mass. There was, however, some increased radiance in this portion of the lung, suggesting air trapping. Seven months before admission, the mass was about half its size on entry and had a similar structure and appearance. In films taken with the patient lying on his back, in other hospitals and here, a widening of the second interspace in the axillary line was evident.

There was no evidence of a destructive process in the ribs in any of the films, and no visible calcification within the mass.

Each day, the sputum was dark reddish brown, and the patient said it had been exactly similar for the past eight months. The pain in his arm grew worse, and was no longer controlled by aspirin and codeine. On the ninth hospital day, constriction of the left pupil was noticed for the first time. The next day, an operation was performed.

Differential Diagnosis

Dr. Theodore L. Badger:* May we see the x-ray films?

Dr. Aubrey O. Hampton: This first examination was made in 1938, when the chest was considered normal. There might be the slightest variation in density between the lung apices, the left being thought by some observers to be a little more radiant than the right. This next film, which was taken two years and two months later, shows a fairly homogeneous dense shadow occupying the region of the left upper lobe, with perhaps a little mottling. There is no displacement of the trachea and no disease in the ribs. The remainder of the lung fields is clear. Still later films show little or no increase in the total size of the mass, but the mottling has become more prominent and there is a strong suggestion of cavitation. These are laminographic films, and this is the same area seen on the plain film. The inferior margin of the shadow is sharp, and within it there are mottled 1-cm. to 2-cm. areas of rarefaction, which are almost like a cluster of grapes, very regular in size. Another significant finding is an unusually straight bronchus, which looks as though it were being pulled on and runs into the area of disease. It filled irregularly with lipiodol. No lipiodol entered the area of disease, and the trachea and main bronchus were not pressed on. In summary, the film shows a fairly sharply defined shadow continuous with the ribs and the apex of the lung and, in the lower portion, multiple cavities of almost the same size. There is also a straight rather drawn-out looking irregular bronchus.

Dr. Badger: Summarizing briefly this complicated and rather difficult case, the outstanding features of the history are two years of fatigue, and hemoptysis eight months before entry. At that time, a diagnosis of tuberculosis was made, followed by hospitalization, and a careful study, which, so far as I can tell, very definitely ruled out tuberculosis. I have no idea what the final diagnoses on discharge from the sanatorium were, except that fungous infection was considered. The patient returned to work four months later and remained there for two months, after which he was forced to retire. Eight weeks before admission, he developed a dull aching pain in the left chest; night sweats also appeared. The pain was in the axilla and radiated down to the forearm. The patient had fever and lost 10 pounds in weight.

Examination was negative except for local findings in the upper third of the left chest, with dullness and diminished breath sounds. No rales could be heard.

The blood and laboratory findings were entirely negative. X-ray study showed the findings that have been pointed out. The patient had, in addition, a final appearance of Horner's syndrome. It was not a complete Horner's syndrome, at least according to physical examination, since only the smallness of the pupil on the left side was noted. Nothing is said of lidlag or of enophthalmos, both of which are customarily seen with Horner's syndrome.

Our problem is to decide whether this is infection or tumor, and if it is tumor, whether it is a growth within the lung itself. The recurrence of symptoms eight months before entry, with dull pain in the shoulder, is not characteristic of tuberculosis or of any infection. I am inclined to rule out infection, which if present does not seem to be an important part of the picture, and believe that we are dealing with a tumor mass within the chest.

The pain in the upper left chest, the radiation of pain down the arm and the development of a Horner's syndrome immediately make us wonder whether we are dealing with a Pancoast tumor. Pancoast,† in his original description in 1924, reported 4 cases, in 2 of which autopsies were performed. Both were first thought to be epitheliomas but were finally diagnosed as squamous-cell carcinomas. Pancoast defines this particular tumor clinically. It must be an extrapulmonary tumor and must show no evidence of origin from the lung or bronchus. It must present erosion of the bone, in addition to pain in the shoulder and axilla that radiates down the arm, with wasting of the muscles of the hands. In all Pancoast tumors, small shadows in the far apex of the lung are visible by x-ray examination.

We must distinguish between the Pancoast tumor and the Pancoast syndrome, which we know today is caused by tumors other than those he originally described. Pancoast's final analysis was that the tumors that arose outside the

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†Pancoast, H. K.: Importance of careful roentgen-ray investigations of apical chest tumors. *J. A. M. A.* 83:1407-1411, 1924.

thorax, in the superior pulmonary sulcus, originated from embryonic rests of the fifth bronchial cleft. Other conditions will produce the syndrome. They may be tumors arising in the spinal canal from the meninges, or metastatic lesions in the lymph nodes of the neck. These can be fairly well ruled out in this case. Therefore, I get the impression that we are dealing with an intrathoracic and intrapulmonary tumor, rather than extrapulmonary tumor of the Pancoast type.

If we believe that we are dealing with a tumor within the chest, what is our diagnosis? Is this a benign tumor or a malignant one? The character of the x-ray shadow is certainly suggestive of something with a sharply defined border, which was progressive in size and which was certainly not destructive, so far as the bone was concerned. The tumor mass invaded vital structures outside the lung itself and must have involved the dorsal sympathetic chain and dorsal roots of the eighth cervical nerve or the brachial plexus itself to account for pain that went down the arm. Neurofibroma might be considered. A benign tumor causing little or no bony destruction may produce a Horner's syndrome and could account for the symptoms presented here. It might be endothelioma. Pancoast thought that his original tumors were endotheliomas but changed his mind. They may appear in the pleura, may invade lung tissue and may cause symptoms like those seen in this case.

Fibrosarcoma or any variety of sarcoma might possibly explain the character and symptoms of this tumor. But this tumor appears primarily as apical and less mediastinal, where the fibrosarcomas commonly arise. I do not believe that any of these tumors explain the symptomatology. I think the first two symptoms of importance in this case are pain extending down the shoulder and arm, and hemoptysis. With the presence of hemoptysis, we must presuppose that there is somewhere a lesion in this patient developing within the bronchus or eroding the bronchus and causing an intraluminal lesion that produced the symptoms. We come down to the final diagnosis, which is certainly not Pancoast tumor. It is my impression, from the early history of hemoptysis and pain in the chest and arm, that we are dealing with bronchiogenic carcinoma of the apex of the lung, in the upper-lobe bronchus. It grew relatively slowly, and was most likely a squamous-cell carcinoma, showing some necrosis in the center to account for the areas of rarefaction. There must have been involvement of the dorsal chain, of the left second and third ribs and invasion of the eighth cervical nerve or of the bronchial plexus itself.

DR. DONALD S. KING: As Dr. Badger has said, the important thing was the dark-red sputum every day for eight months, which rarely occurs, except with bronchiogenic carcinoma.

DR. EDWARD D. CHURCHILL: One of the presenting clinical manifestations in this case was the well-being of the patient, who had no cachexia and no sign that is ordinarily seen with long-standing illness. The point in differential diagnosis that puzzled me most was the choice between a true intrapulmonary malignant tumor and one arising outside the lung. We might have gained some more information by an artificial pneumothorax, but since the question of operability required an absolute answer, we went ahead with exploratory thoracotomy, with the provisional diagnosis of primary bronchiogenic carcinoma invading the chest wall. The pain in the arm was interpreted a bit differently from the way in which Dr. Badger analyzed it, possibly because we could determine that it was sharply localized to the distribution of the axillary branch of the second intercostal nerve. The statement that the pain was below the elbow was, I believe, incorrect. Cancer, with unmistakable evidence of nerve involvement, is usually out of bounds surgically. This proved to be so when the tumor was disclosed at operation. The growth invaded the chest wall and was clearly of intrapulmonary origin. A frozen-section biopsy confirmed the diagnosis of carcinoma.

The problem was one of palliation rather than cure. We know from having seen a great many of these patients with apical carcinoma that the pain in the terminal stages is one of the worst experiences that a person must endure. There has been no way of relieving this pain by section or injection of nerve roots, and the only thing possible is high chordotomy, with its attendant hazards not only to life but loss of sphincter control and other disagreeable sequelae. In spite of the fact that the tumor had invaded the chest wall and despite the fact that there was an involved lymph node 2 cm. in diameter in the anterior mediastinum, the lung in this case was removed, with the hope that we should then be able to give effective deep x-ray therapy to the chest wall. X-ray therapy with the huge tumor in situ might well have produced necrosis, sequestration and secondary infection of the necrotic tumor mass. The hilum of the lung was free and contained grossly no involved lymph nodes, so that the left lung was removed.

The subsequent story is of interest because the patient recovered very rapidly from the operation, and deep x-ray therapy was started with the million-volt machine. He had a little more nausea than usual with that method of treatment. One day, he complained of wax in his ear and said that he had had it removed before by irrigation. From then on, there was a rapid progression of signs of an intracranial lesion, and he was dead within three days.

I think one of the important points in the history of this case is the negative needle biopsy. Too much weight was placed on a negative finding as evidence against neoplasm.

Clinical Diagnosis

Primary bronchiogenic carcinoma invading the chest wall.

Dr. Badger's Diagnosis

Primary bronchiogenic carcinoma of the lung, originating in the left upper-lobe bronchus, presenting a Pancoast syndrome and invading the eighth cervical nerve or the brachial plexus, or both.

Anatomical Diagnosis

Bronchiogenic carcinoma, undifferentiated, left lung.

Pathological Discussion

Dr. Tracy B. Mallory: The tumor occupied the posterior half of the left upper lobe. Most of the growth was posterior rather than anterior. It showed extensive necrosis, and in some places the necrotic areas had broken down completely to form the small cavities that Dr. Hampton demonstrated in the films. From the microscopic point of view, it was an extremely undifferentiated tumor, which one would expect to spread with great rapidity.

Dr. Churchill: Did you find any hilar nodes involved microscopically?

Dr. Mallory: I think not.

Dr. William B. Breed: What kind of tumor was it?

Dr. Mallory: I presume that it was a squamous-cell carcinoma. Certainly, it was an epithelial tumor, but too undifferentiated for exact classification.

CASE 27392*

Presentation of Case

A four-day-old white female infant was brought to the hospital because of blood-stained vomitus of two days' duration. She was the first child of healthy young parents, and was delivered normally at full term. Her birth weight was 8 pounds, 10 ounces. At birth, she cried well and was active, and she later nursed well. During the first day, water was given on four occasions and was immediately followed by vomiting of grayish material.

Two days before entry, a large dark blood clot was vomited. Following this, vomiting after each feeding that day was blood streaked. The day before entry, bright-red blood was vomited twice. Each day the patient passed three or four soft, dark-green stools. There was no bleeding elsewhere at any time.

Physical examination revealed a well-developed, well-nourished active infant who did not appear to be ill. The head, neck, chest, heart and lungs presented no abnormal features. There was no adenopathy. The skin was of good texture and elasticity, and was free of pigmentation, rashes and petechiae. The abdomen was protuberant, with bulging in the left flank. It was rather tense. A large, firm, easily movable mass was felt occupying the entire left flank. The medial border of this mass extended to the umbilicus, and was notched in the central portion. The liver border was smooth and extended 2 cm. below the costal margin in the mid-clavicular line. No other organs or masses could be made out. The genitalia, anus and extremities were normal. All the reflexes were physiologic.

The temperature, pulse and respirations were normal.

Examination of the urine was negative except for 4 or 5 white blood cells per high-power field. Examination of the blood showed a red-cell count of 4,860,000 with 100 per cent hemoglobin, and a white-cell count of 8900 with 32 per cent polymorphonuclears, 54 per cent lymphocytes, 6 per cent monocytes, 4 per cent eosinophils and 1 nucleated red cell per 100 white cells. Bleeding and clotting times were normal. Seven stools were examined, and each was negative for blood.

X-ray studies revealed slight hazy congestion of the chest, a soft-tissue mass in the left side of the abdomen, and normal long bones. Pyelograms showed good excretion on the right, but none from the left kidney.

The patient remained on the ward six days, dur-

*This case is presented through the courtesy of the Children's Hospital.

ing which her temperature was normal and her weight constant. She vomited several times, but the vomitus was never blood stained.

Abdominal exploration was carried out on the sixth day.

Differential Diagnosis

Dr. Margaret Glendy: This baby was brought to the hospital because of blood-stained vomitus. According to the history the vomiting of blood occurred only on two days — the third and fourth days of life. The most frequent cause of vomiting in the newborn infant is hemorrhagic disease. There may have been a slight tendency toward hemorrhagic disease in this case, but it was certainly not very great. The baby may have been breast fed, and some of that blood may have come from cracked nipples, but a large dark-red clot would have been most unusual. The other thing that one would wonder about even in a newborn baby is vomiting from esophageal varices. Several stool examinations were made between the fourth and tenth days of life, and none showed any blood. They may not have been examined at the beginning of the hospital stay. Obviously, there was no gastrointestinal obstruction, and the stool formation was fairly normal, because it is not commented on after the passing of the meconium.

The outstanding abnormal finding in this record is the mass in the left flank. Apparently, it did not extend beyond the mid-line. There was a bulge in the flank, but no comment of any bulging posteriorly in the loin. Taking the meaning of the words literally, I am inclined to think first of all of an enlarged spleen. With an enlarged spleen, the first thing that comes to mind is erythroblastosis fetalis. This baby's blood smear showed only one nucleated red blood cell per 100 cc. Also, there is no comment that the vernix was golden yellow, and no mention of a large heart; a scarred placenta is not mentioned. Nothing is known about the nationality of the parents, so far as the late type of erythroblastic anemia is concerned. The spleen might have been enlarged because of sepsis, but there was no fever and no leukocytosis, and the differential count of the fifth or sixth day is not abnormal. The spleen might have been enlarged because of congenital syphilis. However, x-ray examination of the long bones was negative. No mention is made of the mother's blood Hinton reaction. Nothing is said about parasites in the blood smear. The baby might have had congenital malaria. I do not believe that she did, however. She had no temperature rise in ten days, but the absence of temperature rise does not preclude the possibility of infection or even sepsis in a newborn infant.

I am not certain about the urinary-tract examination. The pyelogram showed no excretion from the left kidney. On the basis of one pyelogram, I am not convinced that the tumor was renal in origin. There may have been only one kidney, but it may be that in the x-ray film the density of the mass in the left flank made the slight amount of concentration of the dye in the pelvis invisible. If this were a kidney tumor of a nonfunctioning kidney, one would expect to find a rather round mass, and one would also expect to find some mass in the loin. Polycystic kidneys are usually bilateral. Solitary cysts of the kidney are, statistically speaking, more frequent on the right than on the left. The Wilms tumor is the most usual kidney tumor in childhood. Sarcoma of the kidney might have invaded the vena cava in utero, producing obstruction and hence collateral circulation and bleeding from varices. Another thing against kidney tumor is the statement that the tumor was freely movable.

Abdominal exploration was carried out. One would not operate on a baby with a large spleen just because it extended from the brim of the pelvis to the thoracic cage. One would operate because there was something there that might interfere with the existence of that child. I have not seen the x-ray films, but my conclusion is that this baby had neoplasm of the spleen. I do not know what the type of growth was.

Dr. Tracy B. Mallory: Should you care to see the x-ray films?

Dr. Glendy: I should like to very much.

Dr. James R. Lingley: The x-ray films are quite helpful in this case, I think. They show quite definitely that this was a tumor of the kidney and not of the spleen, because on the plain film one can see a perfectly normal spleen above the mass that occupies the whole flank. This mass is very large, extending from under the costal border to the crest of the ilium and well over to the mid-line. The pyelogram shows a normal kidney on the right, with good excretion of the dye and absolutely no excretion on the left side. So that I consider the x-ray evidence definitely in favor of a tumor of the kidney. The lungs show nothing definite.

Dr. Mallory: Do you want to accept the x-ray evidence, Dr. Glendy?

Dr. Glendy: Certainly; I am very grateful for it.

Dr. Mallory: It is not always wise.

Dr. Glendy: May I ask why they operated?

Was the baby not doing well from any other point of view?

DR. SIDNEY FARBER:* No; they operated for one good reason: the nature of the large firm mass in the left flank could not be determined without surgical intervention.

DR. FLETCHER H. COLBY: In babies with enlarged spleens, do you ever find that the enlargement is sufficient to cause nonfunctioning of the kidneys? Does it always cause displacement, but not nonfunctioning?

DR. FARBER: Disturbance of kidney function caused by an enlarged spleen must be extremely rare.

CLINICAL DIAGNOSIS

Hemorrhage into left adrenal gland.

DR. GLENDY'S DIAGNOSIS

Congenital tumor in left flank, probably arising from spleen.

ANATOMICAL DIAGNOSIS

Neuroblastoma sympatheticum of left adrenal gland.

PATHOLOGICAL DISCUSSION

DR. FARBER: Many years ago, I learned by sad experience that it was unwise to take too seriously clinical palpation of the notch of the spleen as evidence that a mass in the abdomen represented the spleen. The report in the history of the palpation of a notch was definitely misleading. The patient under discussion today was seen in 1933. For that reason, no information such as might be obtained today concerning the nature of the hemorrhagic episode observed soon after birth is available. I believe that Dr. Glendy's choice of hemorrhagic disease with spontaneous improvement is probably the correct explanation for the vomiting of blood. The surgeon, Dr. George Cutler, resorted to operation because the nature of the large mass that was palpated could not be determined by any clinical or roentgenologic method of study with any degree of accuracy. The clinical diagnosis was massive adrenal hemorrhage. The presence of a malignant tumor was suspected. At operation, Dr. Cutler removed a mass that lay immediately above the left kidney replacing the adrenal gland. It was completely encapsulated and could be stripped without difficulty from the surrounding structures. It weighed over 100 gm. and was round and smooth, and the capsule was intact. The cut surface disclosed a mass divided into a number of lobules containing hemorrhagic necrotic tissue. The final pathological diagnosis was neuroblastoma sympatheticum, which had undergone extensive hemorrhagic necrosis.

The subsequent story may be of some interest. The infant recovered soon after the operation; eight years after that procedure, the child is still alive and in good health. Certainly, the patient has passed far beyond the point where metastasis or recurrence might be expected. I might add that no radiation or any other treatment directed at the tumor was employed at any time.

I should like to make some remarks concerning one of the questions that arose in the matter of differential diagnosis. The pyelogram is of no real aid in the accurate diagnosis of tumors of the kidney region in early life, and may indeed mislead the surgeon if too much reliance is placed on interpretation of the x-ray films. In the first place, it is impossible to tell by means of the pyelogram whether the tumor is within the kidney or within the adrenal gland, or whether the tumor is unattached in the region of the kidney. A neuroblastoma arising from the adrenal medulla may cause just as much obstruction to the ureter as an embryoma arising within the kidney. Furthermore in 3 cases, I have seen a neuroblastoma arise from an adrenal gland in which the growth rested within the substance of the kidney and was responsible for an x-ray picture and a gross pathologic specimen that could not be differentiated from an embryoma of the kidney. In the second place, it is of little importance to know before operation whether the mass is within the kidney or in the immediate vicinity of the kidney. The exact location of the tumor must be determined by the surgeon at the time of operation. The only real use for a pyelogram in infants or children suspected of having a tumor in the kidney region is to provide an easy method of demonstrating that two kidneys are present, in the event that the surgeon must remove one kidney with the tumor.

A second point worthy of special emphasis concerns the reason for operation and exploration of the abdomen of this young infant in whom the main finding was a mass in the abdomen. For many years, we have been guided by Dr. S. Burt Wolbach's generalization concerning tumors of early life, which has been well borne out by repeated tests. This is: *every solid mass in early life is to be regarded as a malignant tumor until*

*Assistant professor of pathology, Harvard Medical School; pathologist, Children's Hospital.

proved otherwise by pathological examination. Although blanket rules are at times quite dangerous, this generalization has settled many a discussion concerning the proper method of treatment in problems of this kind and has not led us into erroneous or harmful decisions.

By neuroblastoma sympatheticum I mean the malignant variety of the series of tumors arising in the sympathetic nervous system. The true nature of this tumor, incidentally, was demonstrated at the Massachusetts General Hospital by Dr. J. Homer Wright in 1911. In a series of 40 neuroblastomas, which occurred in a ten-year period at the Boston Children's Hospital, more than half arose in situations outside the adrenal medulla. About one fourth of these 40 patients are alive and apparently well after operative removal of the tumor and histologic verification of its nature. The tumor is extraordinarily radiosensitive. In 2 cases, cures have been obtained by means of radiation therapy after metastases to the liver had been proved by histologic study. My experience in recent years has led me to conclude that the opinion in the literature concerning the almost universally bad results with the neuroblastoma is not a correct one. At the present time, the method of choice in the treatment of the neuroblastoma is removal of the primary tumor, with subsequent radiation of the area involved by the tumor. Radiation therapy should also be applied to areas involved by metastatic tumor.

A PHYSICIAN: How often are tumors of the adrenal gland as readily movable as the one described in this case?

DR. FARBER: Not often. If the tumor is readily movable, it is more apt to be one arising in the periadrenal tissues rather than in the adrenal gland or in the kidney tissue.

A PHYSICIAN: Was the kidney involved?

DR. FARBER: No; it was just pushed aside by the tumor mass.

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COMBINED SEROTHERAPY AND CHEMOTHERAPY IN PNEUMONIA

Since the introduction of effective sulfonamide drugs, the question of whether specific antipneumococcus serums have any further place in the treatment of pneumonia has been the subject of great controversy. Most physicians may no longer consider this problem of any importance, since they are only occasionally called on to treat patients who are severely ill with pneumonia, and since they have already had an opportunity to convince themselves of the effectiveness of sulfapyridine and sulfathiazole in their cases.

Physicians who treat large numbers of cases, however, are still confronted with some patients whose response to drug treatment is not entirely satisfactory. There are two schools of thought with respect to the additional use of serum in these cases. In one group are those who, like Janeway and Beeson,[1] believe that the additional use of serum in such cases increases the chances for recovery and shortens the duration of acute illness. They recommend the combined use of chemotherapy and serotherapy as the most satisfactory form of treatment in severe pneumonia. In the other group are a large number with a growing conviction that serums have little or nothing to offer in cases in which sulfonamides alone fail. Each of these views has had strong support from controlled clinical studies, which have been recently published. Two reports in particular may be mentioned.

Dowling, Abernethy and Hartman[2] studied a series of patients with Type 1 through Type 8 pneumonias who were alternated for treatment with sulfapyridine alone and with sulfapyridine in addition to specific antipneumococcus serum. Treatment was begun in each therapeutic group as soon as the type was determined. The mortality rate was 12.5 per cent in the group receiving sulfapyridine alone, and 9.8 per cent in the group receiving serum and sulfapyridine. When the Type 3 cases were omitted, the mortality was 9.2 per cent in patients treated with the drug alone and 4.5 per cent in those who received serum in addition. Serum was found to be particularly valuable as an adjunct to sulfapyridine in patients over forty years of age. Crisis occurred more frequently and was prompter in the patients receiving serum in addition to sulfapyridine. These authors suggested that the combined use of serum and chemotherapy be given to patients with pneumonia who are over forty years of age and also to those who are in need of a prompt defervescence.

Those who are not enthusiastic about the use of serum and who consider that its cost and the additional expenditure of the time and effort required in its use are not justified by the additional benefits to the patient may take solace in a re-

port by Plummer and his associates[3] at Bellevue Hospital. These authors used a number of sulfonamides and alternated all patients for treatment by type between chemotherapy with one of these drugs alone and combined chemotherapy and serotherapy. In this study, the results were the same in both groups, regardless of whether the patient was treated early in the disease, whether bacteremia was present, whether the patient was old, and whether systemic disease was present. The authors are, however, willing to concede, "There will probably be no disagreement with the statement that serum should be used for patients who cannot tolerate the sulfonamide drugs or for those who fail to respond satisfactorily within twenty-four to forty-eight hours to drug therapy." They also mention that in their private practice they have used serum several times with gratifying results for patients who failed to respond to chemotherapy, although obviously they cannot say whether these patients would not eventually have recovered without the use of serum.

Finland, in this issue of the *Journal*, points out some of the difficulties involved in carrying out carefully controlled clinical studies on the use of serums. A number of the pitfalls in the Bellevue study are mentioned, and many more can be found on careful perusal of the data presented. Certain important information is also lacking. In particular, the alternation of cases by type could not have been so strict as the authors claim and yet have the series end with 6 more Type 2 patients and 4 more Type 13 cases in one or the other of the two groups. Furthermore, drug treatment was started in all cases immediately, and alternate patients were placed in the serum-plus-drug groups after the type was determined, regardless of whether it was unnecessary to administer serum, because the patient was dead or well. It is stated that the interval between the start of the drug treatment and the time serum treatment was begun was "usually within the first twenty-four hours." Since it is known, however, that the vast majority of patients with pneumonia who eventually respond to chemotherapy already give clear evidence of a favorable response within this period, it is obvious that those who actually received serum were, in most cases, the patients who had responded poorly to chemotherapy.

Although the conclusions drawn by the Bellevue workers from these cases may or may not prove to be correct, Finland points out that the results of studies of this sort are "not only inconclusive but even grossly misleading," since they make unwarranted claims of scientific control. The results here, as in many other studies, are influenced by important factors in the choice of cases that are either unrecognized or merely ignored. Obviously, the "choice" is usually exercised unconsciously.

Combined serotherapy and chemotherapy will certainly not be used routinely by the vast majority of physicians. It is only in the severe cases and in those patients who are unable to tolerate the sulfonamides that the early use of serum in addition to the drug is justified. The usefulness of serum when the drugs fail is generally conceded.

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DIRECTORY OF MEDICAL SPECIALISTS

THE second edition of the *Directory of Medical Specialists*, which will be ready for distribution in February, 1942, will list the names of approximately 18,000 diplomates of the fifteen American boards that examine candidates for certification in the specialties; this is 4000 more than were included in the first edition, which was published early in 1940.

The geographic grouping will give completely revised biographic data about each diplomate, including much information not found in the first edition, such as military appointments and the details of formal training. In addition, the plan of organization, the officers and the examination

requirements of each American board will be fully outlined.

The *Directory* again presents a list of physicians and surgeons who have had excellent training and adequate experience in their chosen fields and who have limited their practice to those fields. This official record of specialists is invaluable as a reference: it provides essential data concerning qualified specialists throughout the United States and Canada, information that is extremely useful to the officers of medical societies and to physicians who refer patients to associates in distant communities.

The new edition will probably be as much in demand as its predecessor, which had a wide distribution, not only among the members of the medical profession and medical libraries, but also among insurance companies and firms that manufacture and distribute medical supplies.

MEDICAL EPONYM

Kernig's Sign

Vladimir Michailovich Kernig (1840–), ordinator at the Obuchow Hospital in St. Petersburg, reported "Ueber ein wenig bemerktes Meningitis-Symptom [A Little-Noticed Symptom of Meningitis]" in the *Berliner klinische Wochenschrift* (**21:** 829–832, 1884). A portion of the translation follows:

> For a number of years, I have noticed in the cases of meningitis that have come under my attention a symptom that seems to be little known, although in my opinion it has a definite, practical value. I refer to the occurrence of a flexion contracture in the legs, occasionally occurring also in the arms, which is first seen when the patient sits up. . . . If the patient sits on the edge of the bed so that the legs hang over (in cases with very marked stiffness of the neck and back this is not easily accomplished), the contracture of the neck and back usually becomes much more marked. *Furthermore, there is now observed a flexion contracture in the knee joint and occasionally, also, in the elbow joint.* Extension of the patient's leg at the knee is now only possible to an angle of about 135°, or if the phenomenon is marked, only to a right angle. . . . I am also convinced that, with the patient in the dorsal position, this contracture appears when the extended leg is brought to a right angle with the trunk. In normal patients, no similar contracture is seen with the same degree of flexion of the hip.
>
> R. W. B.

MASSACHUSETTS MEDICAL SOCIETY

SECTION OF OBSTETRICS AND GYNECOLOGY*

Fatal Diabetic Coma in Pregnancy

A thirty-year-old para II was first seen when she was approximately thirty-two weeks pregnant. She had had diabetes for ten years and had been followed by a hospital clinic. She had always been most unco-operative and had been in the hospital in diabetic coma twelve times prior to the present admission. The previous pregnancy terminated in a premature breech delivery at six months. The baby was stillborn, and the patient herself was in diabetic coma.

The patient was kept in the hospital about three weeks. At the end of this time, since she was somewhat over thirty-six weeks pregnant, it was decided to deliver her by cesarean section and sterilize her. She was presumably in good condition from the standpoint of the diabetes on the morning of operation. After the administration of 3 gr. of Nembutal and 15 cc. of paraldehyde in oil, she was taken to the operating room. Her condition suddenly became extremely serious, and the blood pressure dropped to 82 systolic, 50 diastolic, and the pulse rose to 172. The operation was postponed, and on the same afternoon the blood pressure rose very suddenly to 202 systolic, 90 diastolic. The patient developed a right-sided facial paralysis and died undelivered.

Comment. Pregnancy in diabetes is much more frequently seen than it was in the preinsulin days, and a death such as this should be extremely unusual. Well-organized diabetic clinics have no fear for the mother's life. Not yet can a living baby be guaranteed in every diabetic pregnancy. It is true that this patient was most unco-operative, but in the light of the experience of other diabetic clinics it does seem that this maternal death could be attributed solely to unskilled handling of the diabetic problem. The average practitioner has learned that insulin almost always controls diabetes very easily. The average diabetic specialist who has not seen much of the complication of pregnancy does not appreciate the instability that pregnancy places on these patients. This can fairly be called a preventable death. If deaths occurring in diabetic patients during pregnancy are to be prevented, the pregnancies of these patients must be handled by trained diabetic specialists and those who have had particular experience in handling the problem.

*A series of selected case histories by members of the section will be published weekly. Comments and questions by subscribers are solicited and will be discussed by members of the section. Letters should be addressed to Dr. Raymond S. Titus, *Secretary*, 330 Dartmouth Street, Boston.

DEATH

FULLER — Ernest P. Fuller, M.D., of Lawrence, died September 14. He was in his sixty-ninth year.

Born in North Andover, he graduated from New York University College of Medicine in 1899. Dr. Fuller was on the staff of the Lawrence General Hospital, and was a fellow of the Massachusetts Medical Society and the American Medical Association. He held memberships in the Lawrence and North Essex medical clubs.

His widow, a daughter, three grandsons, three sisters and a brother survive him.

NEW HAMPSHIRE MEDICAL SOCIETY

DEATHS

ABBOTT — Charles B. Abbott, M.D., of Hillsboro, died March 24. He was in his seventieth year.

Dr. Abbott, the son of Benjamin and Mary (Choate) Abbott was born in Bradford and graduated from Dartmouth Medical School in 1902. He was a member of the New Hampshire Medical Society.

He is survived by his widow and a sister.

WEINBERG — Philip B. Weinberg, M.D., of Whitefield, died August 27. He was in his fifty-fourth year.

Born in Berlin, Germany, Dr. Weinberg received his degree from Tufts College Medical School in 1920. He was a member of the New Hampshire Medical Society and the American Medical Association.

He is survived by his widow, three brothers and three sisters.

CORRESPONDENCE

COMBINED SEROTHERAPY AND CHEMOTHERAPY IN PNEUMONIA

To the Editor: In the paper entitled, "Controlling Clinical Therapeutic Experiments with Specific Serums," which appears in this issue of the *Journal*, is included a criticism of a study that was published from Bellevue Hospital. In view of this, I took the liberty of sending a copy of the manuscript to Dr. Norman Plummer, prior to publication, and have received the following reply. I believe it is only fair that you publish this letter, and you have Dr. Plummer's permission to do so.

I believe that the arguments brought forth by Dr. Plummer serve only to emphasize the whole theme of my discussion: namely, that it is impossible to carry out large-scale clinical experiments with strictly scientific controls that are not open to criticism. As a single example, if one works out the probability that the difference in the twenty-four-hour deaths in the two groups is a matter of chance, one finds that it is approximately one out of thirty-five times.

It is only because we have ourselves been so thoroughly disillusioned when reviewing the results of our clinical results, which we thought were carefully controlled, that we became convinced of how difficult it is to carry out such experiments.

Maxwell Finland

Boston City Hospital
Boston

* * *

September 11, 1941

Dear Dr. Finland: Your paper arrived a few days ago, and I appreciate your consideration in sending it to me. Perhaps I can clarify some of the points to which you refer in your criticism.

You state, "Some of the patients were already dead and others were afebrile at the time the type was determined; they received no serum, but were nevertheless retained in the group receiving combined treatment." The statement implies that this was not the way in which to handle the alternation of cases. The plan we had in mind from the start was to handle the series as though the patients were being treated in two different hospitals. On the shelves of the one hospital there was a supply of sulfonamide drugs, and on the shelves of the other there were both sulfonamide and serum. Everything else was the same for the two groups of cases. In each series the effort was made to obtain the best results possible under the circumstances of the experiment. We realized that one disadvantage of specific serum was the delay in administration, caused by the time required for typing. It is true that a few (6) patients dying within twenty-four hours were dead before the typing was obtained. Should these cases have been removed from the series? To do so would not be legitimate unless the cases in the chemotherapy-alone series were treated in the same way, and any attempt at such manipulation would certainly be open to criticism. Some patients (actually 95 of the 301 cases) were so fully recovered that, when the typing was obtained, serum was no longer indicated. The serum was available had there been any use for it. What should be done with these cases? To remove them, and to offset this by removing similar cases from the other group, again would be difficult and would be a manipulation of the experiment.

You state, "It is rather odd, in view of the strict alternation in type stressed by these authors, that for many of the types there is a preponderance of cases either in the series treated with the drug alone, or in the combined-therapy series." By this, you refer to there being in Type 2, 49 cases on the one side and 55 on the other; in Type 5, 24 and 27; in Type 13, 5 and 1; in Type 18, 3 and 6; in Type 19, 8 and 5; and in Type 20, 7 and 4. This discrepancy can be quickly explained: while we used strict criteria for making the clinical diagnosis, there were cases included and alternated that, on later analysis, were proved not to have pneumonia. This was particularly striking in Type 2, because during one season there was a high incidence of Type 2 pneumococci in severe upper respiratory infections. Furthermore, our experiment was opened and closed three different years, which again created some of this discrepancy.

Again you state, "The length of the delay before serum treatment was given in most cases is not mentioned. . . ." The typing was done in a pneumonia laboratory by experienced technicians giving a twenty-four-hour service. Emphasis was placed on rapidity and accuracy. The delay in obtaining types was probably equal to that which you encounter on your service and much less than that in the average large hospital. Because of the quality of typing service which we maintained, the results obtained in our combined group should have been better than would have been expected were the typing less efficient.

You continue with this statement, "Furthermore, although mention is made of the number of patients who received serum and died within twenty-four hours, the total number of patients who actually received serum

is not given." You failed to get the important point of our study: namely, that we were not comparing the results with serum and no serum, but the results in a series of having the benefits of both drug and serum with those in a series having only the drug. Actually 62.4 per cent of the patients in the serum series received serum, and only 6 of the cases due for serum died before it could be given.

Your next statement is, "Moreover, a considerable portion of the mortality among the patients who received combined treatments occurred within twenty-four hours of admission to the hospital, whereas only a small number of those receiving drug alone died within twenty-four hours of entry." This was exactly the way the series turned out, and it shows how the laws of chance operate in such a study. The fallacy of including the twenty-four-hour deaths is well recognized, and that is the reason why we show these cases apart from the rest of the series.

You further state: ". . . it seems much more probable that some unconscious selection on the part of the authors played an important role in the inclusion of the poorest subjects among the serum recipients. This is only a natural occurrence, since there is always a tendency to give to the patients who seem the most severely ill the benefits of any remedy that is known to be effective." We avoided such a possibility by taking a number of precautions. There were a number of physicians treating the patients, and they had nothing to do with the alternation of the cases. This was done in the laboratory by the technicians, who again had no knowledge whatever of the clinical condition of the patients. Furthermore, the serum was kept in the laboratory and delivered to the ward when a serum case was discovered. On this basis, how there could have been a conscious or unconscious selection, I am at a loss to explain. With such criticism as you did offer you must consider the possibility of manipulation at the time the list was compiled. Actually, the list was compiled by seven different persons, and at the time the columns were added no one had the slightest conception of how the series turned out.

Finally, you conclude, "The conclusions drawn by these authors may or may not prove to be correct, but one cannot help believing that the results as presented are not only inconclusive but are even grossly misleading." If you will reread the paper, you will note that we avoid sweeping conclusions.

I was amused at your final paragraph, in which you say, "It is my opinion that this particular question as it concerns pneumonia is now a highly academic one, since it is unlikely that any physician would contemplate using the combined therapy as a routine in all cases." Originally, we concluded our paper with: "Our results indicate that serum no longer plays a role in the routine treatment of pneumonia," but we thought that this statement was too strong. In presenting our study, we had no desire to draw conclusions, but we did make every effort to tabulate our results as accurately as possible. The omission of the figures mentioned by you was not done to mislead anyone, but to make the article as concise and brief as possible. There was not a single individual in our group who had a preconceived opinion regarding the outcome of the investigation. All of us had used serum enthusiastically and had no reason to oppose its use. Furthermore, our active group received constant counsel from the directors of our divisions, Dr. Cecil and Dr. Sutliff, and it hardly seems possible that they would allow us to be so "grossly misleading."

I have tried to answer your criticism as completely as possible, but if there is any point which is not entirely covered, I shall be pleased to discuss it further with you.

Yours sincerely,

NORMAN PLUMMER

The New York Hospital
New York City

NOTICES

ANNOUNCEMENTS

DR. HILBERT F. DAY announces the removal of his office from 412 Beacon Street, Boston, to 34 Kirkland Street, Cambridge.

DR. LEO J. MCDERMOTT announces the removal of his office from 372 Longwood Avenue, Boston, to 151 Vaughan Street, Portland, Maine.

DR. AUGUSTUS RILEY announces the removal of his office from 868 Beacon Street to 59 Bay State Road, Boston.

JOHN T. BOTTOMLEY SOCIETY

The regular monthly meeting of the John T. Bottomley Society will be held in the Out-Patient Building of the Carney Hospital on Wednesday, October 1, at 11:30 a.m.

Physicians and students are cordially invited to attend.

BOSTON DOCTORS' SYMPHONY ORCHESTRA

The Boston Doctors' Symphony Orchestra will resume rehearsals, under Alexander Thiede, on Thursday, October 9, at 8:30 p.m. at Station WMEX, 70 Brookline Avenue, Boston. Those interested in becoming members should communicate with Dr. Julius Loman, 520 Beacon Street, Boston (KEN 3200 or LON 2155).

CONSULTATION CLINICS FOR CRIPPLED CHILDREN IN MASSACHUSETTS, UNDER THE PROVISIONS OF THE SOCIAL SECURITY ACT

CLINIC	DATE	CLINIC CONSULTANT
Haverhill	October 1	William T. Green
Lowell	October 3	Albert H. Brewster
Salem	October 6	Paul W. Hugenberger
Brockton	October 9	George W. Van Gorder
Gardner	October 14	Mark H. Rogers
Northampton	October 15	Garry deN. Hough, Jr.
Worcester	October 17	John W. O'Meara
Pittsfield	October 20	Frank A. Slowick
Fall River	October 27	Eugene A. McCarthy
Hyannis	October 28	Paul L. Norton

WACHUSETT MEDICAL IMPROVEMENT SOCIETY

The next meeting of the Wachusett Medical Improvement Society will be held at the Holden District Hospital on Wednesday, October 1, at 6:30 p.m. Dr. Richard Schatzki, of the Massachusetts General Hospital, will speak on "X-Ray Examination in Cases of Hemorrhage from the Upper Gastrointestinal Tract."